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(54) Title: ENHANCEMENT OF SLEEP WITH A GROWTH HORMONE SECRETAGOGUE

(57) Abstract

A growth hormone secretagogue is useful, alone or in combination with other agents, for enhancing and improving the quality of sleep, in particular by increasing sleep efficiency and augmenting sleep maintenance.

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TITLE OF THE INVENTION
ENHANCEMENT OF SLEEP WITH A GROWTH HORMONE SECRETAGOGUE

BACKGROUND OF THE INVENTION

Although sleep is necessary for survival, its precise homeostatic contribution is unknown. Sleep is not a uniform state, but rather involves several stages characterized by changes in the individual's EEG. A non rapid eye movement (NREM) type (75 to 80% of total sleep time) ranges in depth through stages 1 to 4 (deepest level). Stage 1 sleep is drowsiness, in which the EEG displays a lower voltage, more mixed frequencies and deterioration of alpha rhythm relative to the EEG when the individual is awake. In stage 2, background activity similar to that of stage 1 is experienced, with bursts of slightly higher frequency "sleep spindles" and sporadic higher amplitude slow wave complexes. The third and fourth stages of sleep display increasing high amplitude slow wave activity. The separate sleep stage in which the individual undergoes rapid eye movement (REM) occupies the remainder of the sleep time and occurs 5 to 6 times during a normal nights sleep. REM sleep is characterized by a lower voltage, higher frequency EEG and other characteristics similar to those which occur when the individual is awake, whereas the other four sleep stages are categorized as NREM sleep.

Individuals vary widely in their requirements for sleep, which is influenced by a number of factors including their current emotional state. The natural aging process is associated with changes in a variety of circadian and diurnal rhythms. Age-related changes in the timing and structure of sleep are surprisingly common problems for older people, and are often associated with significant morbidity. With advancing age, the total amount of sleep tends to shorten. Stage 4 can decrease or disappear and sleep may become more fragmented and

interrupted. Evaluation of sleep patterns in elderly people shows that the timing of sleep is also phase advanced, especially in women. This tendency to go to sleep and wake up earlier is very frustrating to older people who feel that they are out of step with the rest of the world. In addition, the quality of sleep in the elderly is diminished with a marked reduction in slow wave sleep, a reduction in the deep stages of sleep (especially stage 4), fragmentation of REM sleep and more frequent awakenings. Similarly, non-elderly people may exhibit disturbances in the normal sleep process. These changes in the structure of sleep have been correlated to more frequent napping, decreased daytime alertness and declining intellectual function and cognitive ability. Deprivation of REM sleep has been suggested to interfere with the memory consolidation involved in learning skills through repetitive activity, and slow wave sleep has been implicated as being important in consolidation of events into long term memory. Likewise, decreases in the length of REM stages of sleep may be associated with a decrease in cognitive function and learning, especially diminished retention of memory.

Sleep disorders generally involve disturbances of sleep that affect a subject's ability to fall and/or stay asleep, and involve sleeping too little, too much or resulting in abnormal behavior associated with sleep.

Numerous compounds are employed in the art to facilitate normal sleep and to treat sleep disorders and sleep disturbances, including e.g., sedatives, hypnotics, anxiolytics, antipsychotics, antianxiety agents, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents, benzodiazepines, barbituates, 5HT-2 antagonists, and the like. Similarly, physical methods have been employed to treat patients with sleep disorders such as the use of light therapy or the application of modulated electrical signals to selected nerves or nerve bundles.

Nevertheless, the known threapeutic regimens suffer from numerous problems, including residual effects in daytime function, impairment of memory, potential for addiction, rebound insomnia, "REM rebound" which may be associated with increased dream intensity and the

occurrence of nightmares, and the like. Accordingly, a more physiological way to enhance sleep would be highly desirable.

Growth hormone, which is secreted from the pituitary, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic effects on the metabolic processes of the body: (1) Increased rate of protein synthesis in all cells of the body; (2) Decreased rate of carbohydrate utilization in cells of the body; (3) Increased mobilization of free fatty acids and use of fatty acids for energy.

A deficiency in growth hormone secretion can result in various medical disorders, depending on the age of onset. In children, the syndrome is characterized by short stature with normal body proportions and reduced growth rate (dwarfism). A deficiency in growth hormone secretion in adult life may be characterized by excessive adiposity, reduced muscle mass, impaired exercise capacity, reduced body water, decreased bone mineral density, and psychological disorders.

The temporal association of growth hormone secretion and sleep is well established. In particular, growth hormone release and slow wave sleep both predominate in the first part of sleep. Maximal growth hormone secretion is observed during stages 3 and 4 (slow wave) sleep. Additional studies, however, suggest that although slow wave sleep and growth hormone secretion occur simultaneously (and may influence each other), there may be another stimulus or series of neural events which trigger both processes.

A study of the interaction between sleep and growth hormone indicates that subjects with growth hormone disturbances have abnormal REM and delta sleep and that normalization of growth hormone levels corrects the sleep stages (Astrom, Acta. Neurol. Scand., 92, 281-286 (1995); Astrom, et al., Neuroendocrinology, 51, 82-84 (1990)). In particular, young adults with lack of growth hormone compared to normal subjects revealed increased total sleep time, decreased delta sleep time, normal total REM sleep time, and increased stage 1 and stage 2 sleep time. Young adults with high growth hormone concentration (acromegalic) compared to normal subjects revealed decresed REM sleep

time, decresed delta sleep time, and increased stage 2 and stage 1 sleep time. Administration of systemic growth hormone, however, is reported to not affect human sleep (Kern, et al., J. Clin. Endo. Metab., 76, 1428-1432 (1993)). Gamma-hydroxybutyrate has been reported to be useful for increasing slow-wave sleep in patients exhibiting low levels of slow wave sleep (see e.g. PCT Patent Pub. No. WO 96/40105). Effects of oral administration of a growth hormone secretagogue to healthy young men (Copinschi, et al., J. Clin. Endo. Metab., 81(8), 2776-2782) and to healthy elderly subjects have been reported (Chapman, et al., J. Clin. Endo. Metab., 81(12) 4249-4257 (1996).

Various ways are known to release growth hormone. For example, chemicals such as arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known growth hormone secretagogue growth hormone releasing factor (GRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous growth hormone or by administering GRF, IGF-I or a peptidal compound which stimulated growth hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in a very expensive product and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the growth hormone. Recombinant growth hormone has become available which, while no longer carrying any risk of disease transmission, is still a very expensive product which must be given by injection or by a nasal spray. In addition, administration of exogenous growth hormone may result in side-effects, including edema, and does not

correlate with the pulsitile release seen in the endogenous release of growth hormone.

Certain compounds have been developed which stimulate the release of endogenous growth hormone. Peptides which are known to stimulate the release of endogenous growth hormone include growth hormone releasing hormone, the growth hormone releasing peptides GHRP-6 and GHRP-1 (described in U.S. Patent No. 4,411,890, PCT Patent Pub. No. WO 89/07110, and PCT Patent Pub. No. WO 89/07111) and GHRP-2 (described in PCT Patent Pub. No. WO 93/04081), as well as hexarelin (J. Endocrinol Invest., 15(Suppl 4), 45 (1992)).

Growth hormone releasing peptide-6 (GHRP-6) is believed to act via a unique pituitary and hypothalamic receptor and stimulates the release of growth hormone, cortisol and prolactin. In a study in young men, repeated intravenous boluses of GHRP-6 increased stage 2 sleep without affecting slow wave or REM sleep (Frieboes, et al., Neuroendocrinology, 61:584-589 (1995)). Growth hormone-releasing hormone is reported to mediate feeding-specific feedback to the suprachiasmatic circadian clock (Vaccarino, et al., Peptides, 16(4), 595-598 (1995). Although the effects of systemic administration of growth hormone-releasing hormone on sleep are not consistent, episodic administration of growth hormone-releasing hormone is reported to promote slow wave sleep and enhance REM sleep, relative to placebo or continuous infusion of growth hormone-releasing hormone (Marshall, et al., J. Clin. Endocrinol. Metab., 81(3), 1009-1013 (1996)). Nevertheless, a disadvantage of these peptidal growth hormone secretagogues is that they have very low oral bioavailability. Although oral administration of GHRP-2 is under clinical investigation, all of the other peptidal growth hormone secretagogues must be administered parenterally.

Other compounds possessing growth hormone secretagogue activity are disclosed in the following: U.S. Patent No. 3,239,345; U.S. Patent No. 4,036,979; U.S. Patent No. 4,411,890; U.S. Patent No. 5,206,235; U.S. Patent No. 5,283,241; U.S. Patent No. 5,284,841; U.S. Patent No. 5,310,737; U.S. Patent No. 5,317,017; U.S. Patent No. 5,374,721; U.S. Patent No. 5,430,144; U.S. Patent No. 5,434,261; U.S.

Patent No. 5,438,136; U.S. Patent No. 5,494,919; U.S. Patent No. 5,494,920; U.S. Patent No. 5,492,916; U.S. Patent No. 5,536,716; EPO Patent Pub. No. 0,144,230; EPO Patent Pub. No. 0,513,974; PCT Patent Pub. No. WO 94/07486; PCT Patent Pub. No. WO 94/08583; PCT Patent Pub. No. WO 94/11012; PCT Patent Pub. No. WO 94/13696; PCT Patent Pub. No. WO 94/19367; PCT Patent Pub. No. WO 95/03289; PCT Patent Pub. No. WO 95/03290; PCT Patent Pub. No. WO 95/09633; PCT Patent Pub. No. WO 95/11029; PCT Patent Pub. No. WO 95/12598; PCT Patent Pub. No. WO 95/13069; PCT Patent Pub. No. WO 95/14666; PCT Patent Pub. No. WO 95/16675; PCT Patent Pub. No. WO 95/16692; PCT Patent Pub. No. WO 95/17422; PCT Patent Pub. No. WO 95/17423; PCT Patent Pub. No. WO 95/34311; PCT Patent Pub. No. WO 96/02530; PCT Patent Pub. No. WO 96/05195; PCT Patent Pub. No. WO 96/15148; PCT Patent Pub. No. WO 96/22782; PCT Patent Pub. No. WO 96/22997; PCT Patent Pub. No. WO 96/24580; PCT Patent Pub. No. WO 96/24587; PCT Patent Pub. No. WO 96/35713; PCT Patent Pub. No. WO 96/38471; PCT Patent Pub. No. WO 97/00894; PCT Patent Pub. No. WO 97/06803; PCT Patent Pub. No. WO 97/07117; Science, 260, 1640-1643 (June 11, 1993); Ann. Rep. Med. Chem., 28, 177-186 (1993); Bioorg. Med. Chem. Ltrs., 4(22), 2709-2714 (1994); and Proc. Natl. Acad. Sci. USA 92, 7001-7005 (July 1995). Additional compounds with growth hormone secretagogue activity are described herein.

SUMMARY OF THE INVENTION

The present invention is directed to the use of a compound which has the ability to stimulate or amplify the release of natural or endogenous growth hormone or growth hormone-releasing hormone for enhancing or improving sleep quality, in particular by increasing sleep efficiency and augmenting sleep maintenance, as well as for preventing and treating sleep disorders and sleep disturbances, in a warm-blooded animal. The known threapeutic regimens regarding sleep suffer from numerous problems, including residual effects in daytime function, impairment of memory, potential for addiction, rebound insomnia, "REM rebound" which may be associated with increased dream intensity and the

occurrence of nightmares, and the like. An advantage of the present method is that it provides a physiological-like pulsatile profile of growth hormone release from the pituitary gland and further provides for the release of growth hormone-releasing hormone. Accordingly, the present invention provides a method for enhancing or improving sleep quality and increasing sleep efficiency and sleep maintenance in a warm-blooded animal comprising the administration of a growth hormone secretagogue. The present invention further provides a pharmaceutical composition for enhancing or improving sleep quality and increasing sleep efficiency and sleep maintenance.

DESCRIPTION OF THE INVENTION

The present invention is directed to the use of a compound which has the ability to stimulate or amplify the release of natural or endogenous growth hormone for enhancing or improving sleep quality as well as preventing and treating sleep disorders and sleep disturbances in a warm-blooded animal. In particular, the present invention provides a method for enhancing or improving sleep quality by increasing sleep efficiency and augmenting sleep maintenance. In addition, the present invention provides a method for preventing and treating sleep disorders and sleep disturbances in a warm-blooded animal which comprising the administration of a growth hormone secretagogue. The present invention further provides a pharmaceutical composition for enhancing or improving sleep quality and increasing sleep efficiency and sleep maintenance

The following outcomes in a subject which are provided by the present invention may be correlated to enhancement in sleep quality: an increase in the value which is calculated from the time that a subject sleeps divided by the time that a subject is attempting to sleep; a decrease in sleep latency (the time it takes to fall asleep); a decrease in difficulties in falling asleap; a decrease in the number of awakenings during sleep; a decrease in nocturnal arousals; a decrease in the time spent awake following the initial onset of sleep; an increase in the total amount of sleep; an increase the amount and percentage of REM sleep; an increase

in the duration and occurrence of REM sleep; a reduction in the fragmentation of REM sleep; an increase in the amount and percentage of slow-wave (i.e. stage 3 or 4) sleep; an increase in the amount and percentage of stage 2 sleep; an enhancement of EEG-delta activity during sleep; a decrease in the number of awakenings; a decrease in nocturnal arousals, especially early morning awakenings; an increase in daytime alertness; an increased satisfaction with the intensity of sleep; and increased sleep maintenance. Secondary outcomes which may be provided by the present invention include enhanced cognitive function and increased memory retention.

The present invention is further useful for the prevention and treatment of sleep disorders and sleep disturbances including sleep problems associated with insomnia, hypersomnia, sleep apnea, narcolepsy, nocturnal myoclonus, REM sleep interruptions, jet-lag, shift workers' sleep disturbances, dysomnias, night terror, insomnias associated with depression or with emotional/mood disorders, as well as sleep walking and enuresis, as well as sleep disorders which accompany aging. Sleep disorders and sleep disturbances are generally characterized by difficulty in initiating or maintaining sleep or in obtaining restful or enough sleep. Similarly, the present invention is useful for treating conditions associated with circadian rhythmicity as well as mental and physical disorders associated with travel across time zones and with rotating shift-work schedules. In addition, certain drugs may also cause reductions in REM sleep as a side effect and the present invention may be used to correct those types of sleeping disorders as well. The present invention would also be of benefit in the treatment of syndromes such as fibromyalgia which are manifested by non-restorative sleep and muscle pain or sleep apnea which is associated with respiratory disturbances during sleep. In this case, the release of growth hormone associated with the growth hormone secretagogue may also improve respiratory function as a result of increased muscle strength and tone associated with growth hormone release. It will be clear to one skilled in the art that the present invention is not limited to just sleep disorders and sleep disturbances, but

is applicable to a wide variety of conditions which result from a diminished quality of sleep.

In the present invention, it is preferred that the subject mammal is a human. Although the present invention is applicable both old and young people, it would find greater application in elderly people. Further, although the invention may be employed to enhance the sleep of healthy people, it may be especially beneficial for enhancing the sleep quality of people suffering from sleep disorders or sleep disturbances.

By the term "growth hormone secretagogue" is meant any exogenously administered compound or agent that directly or indirectly stimulates or increases the endogenous release of growth hormone, growth hormone-releasing hormone or somatostatin in an animal, in particular, a human.

The growth hormone secretagogue may be peptidal or non-peptidal in nature, however, the use of a non-peptidal growth hormone secretagogue is preferred. In addition, for convenience the use of an orally active growth hormone secretagogue is preferred. In addition, it is preferred that the growth hormone secretagogue induce or amplify a pulsatile release of endogenous growth hormone. It is also preferred that the growth hormone secretagogue be able to cause the release of growth hormone at night or during the sleep cycle, especially in the first half of the night or of the sleep cycle, and even more especially in the first few hours following sleep onset, or alternatively in the period immediately preceding sleep onset.

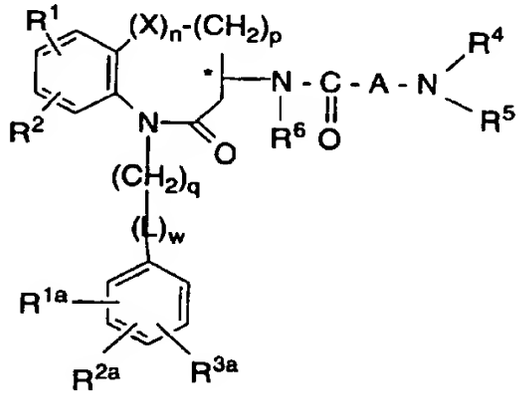
The growth hormone secretagogue may be used alone or in combination with other growth hormone secretagogues or with other agents which are known to be beneficial in the enhancement of sleep efficiency. The growth hormone secretagogue and the other agent may be coadministered, either in concomitant therapy or in a fixed combination. For example, the growth hormone secretagogue may be administered in conjunction with other compounds which are known in the art to be useful for enhancing sleep quality and preventing and treating sleep disorders and sleep disturbances, including e.g., sedatives, hypnotics, anxiolytics, antipsychotics, antianxiety agents, minor

tranquilizers, melatonin agonists and antagonists, melatonergic agents, benzodiazepines, barbituates, 5HT-2 antagonists, and the like, such as: adinazolam, allobarbital, alonimid, alprazolam, amitriptyline, amobarbital, amoxapine, bentazepam, benzoctamine, brotizolam, bupropion, busprione, butabarbital, butalbital, capuride, carbocloral, chloral betaine, chloral hydrate, chlordiazepoxide, clomipramine, cloperidone, clorazepate, clorethate, clozapine, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, estazolam, ethchlorvynol, etomidate, fenobam, flunitrazepam, flurazepam, fluvoxamine, fluoxetine, fosazepam, glutethimide, halazepam, hydroxyzine, imipramine, lithium, lorazepam, lormetazepam, maprotiline, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, midaflur, midazolam, nefazodone, nisobamate, nitrazepam, nortriptyline, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, reclazepam, roletamide, secobarbital, sertraline, suproclone, temazepam, thioridazine, tracazolate, tranylcypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, zolazepam, zolpidem, and salts thereof, and combinations thereof, and the like, or the growth hormone secretagogue may be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation.

Representative growth hormone secretagogues are disclosed in: U.S. Patent No. 3,239,345; U.S. Patent No. 4,036,979; U.S. Patent No. 4,411,890; U.S. Patent No. 5,206,235; U.S. Patent No. 5,283,241; U.S. Patent No. 5,284,841; U.S. Patent No. 5,310,737; U.S. Patent No. 5,317,017; U.S. Patent No. 5,374,721; U.S. Patent No. 5,430,144; U.S. Patent No. 5,434,261; U.S. Patent No. 5,438,136; U.S. Patent No. 5,494,919; U.S. Patent No. 5,494,920; U.S. Patent No. 5,492,916; U.S. Patent No. 5,536,716; EPO Patent Pub. No. 0,144,230; EPO Patent Pub. No. 0,513,974; PCT Patent Pub. No. WO 89/07110; PCT Patent Pub. No. WO 89/07111; PCT Patent Pub. No. WO 93/04081; PCT Patent Pub. No. WO 94/07486; PCT Patent Pub. No. WO 94/08583; PCT Patent Pub. No.

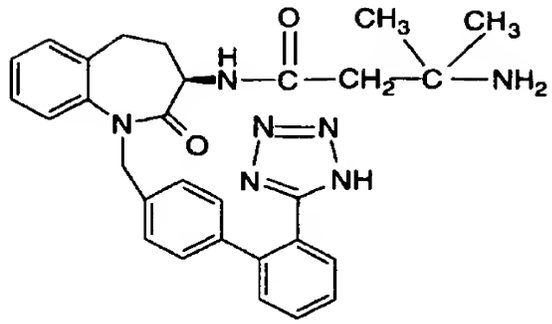
WO 94/11012; PCT Patent Pub. No. WO 94/13696; PCT Patent Pub. No. WO 94/19367; PCT Patent Pub. No. WO 95/03289; PCT Patent Pub. No. WO 95/03290; PCT Patent Pub. No. WO 95/09633; PCT Patent Pub. No. WO 95/11029; PCT Patent Pub. No. WO 95/12598; PCT Patent Pub. No. WO 95/13069; PCT Patent Pub. No. WO 95/14666; PCT Patent Pub. No. WO 95/16675; PCT Patent Pub. No. WO 95/16692; PCT Patent Pub. No. WO 95/17422; PCT Patent Pub. No. WO 95/17423; PCT Patent Pub. No. WO 95/34311; PCT Patent Pub. No. WO 96/02530; PCT Patent Pub. No. WO 96/05195; PCT Patent Pub. No. WO 96/15148; PCT Patent Pub. No. WO 96/22782; PCT Patent Pub. No. WO 96/22997; PCT Patent Pub. No. WO 96/24580; PCT Patent Pub. No. WO 96/24587; PCT Patent Pub. No. WO 96/35713; PCT Patent Pub. No. WO 96/38471; PCT Patent Pub. No. WO 97/00894; PCT Patent Pub. No. WO 97/06803; PCT Patent Pub. No. WO 97/07117; J. Endocrinol Invest., 15(Suppl 4), 45 (1992)); Science, 260, 1640-1643 (June 11, 1993); Ann. Rep. Med. Chem., 28, 177-186 (1993); Bioorg. Med. Chem. Ltrs., 4(22), 2709-2714 (1994); and Proc. Natl. Acad. Sci. USA 92, 7001-7005 (July 1995).

A representative first class of growth hormone secretagogues is set forth in U.S. Patent No. 5,206,235 as follows:

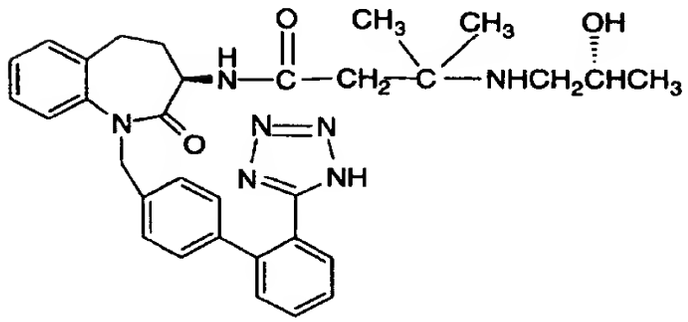


wherein the various substituents are as defined in U.S. Patent 5,206,235.

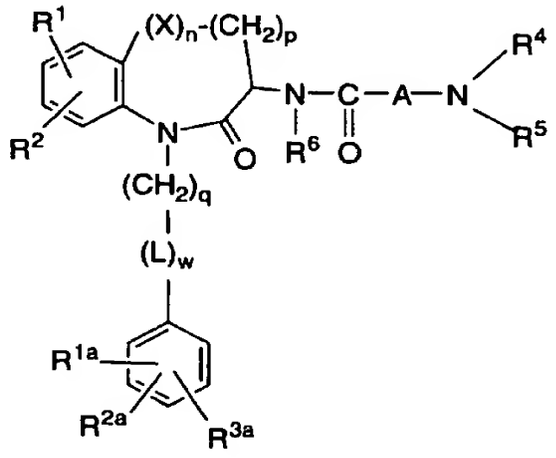
The most preferred compounds within this first class are identified as having the following structures:



or

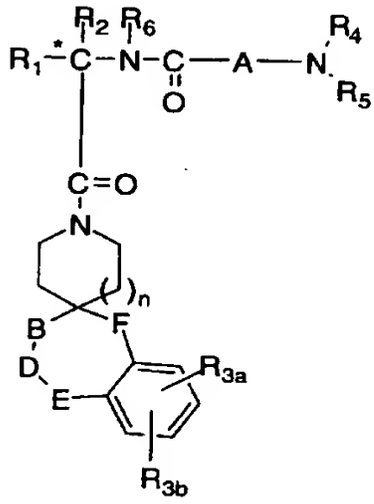


A representative second class of growth hormone secretagogues is set forth in U.S. Patent No. 5,283,241 and PCT Patent Publication No. 94/05634 as having the following structural formula:

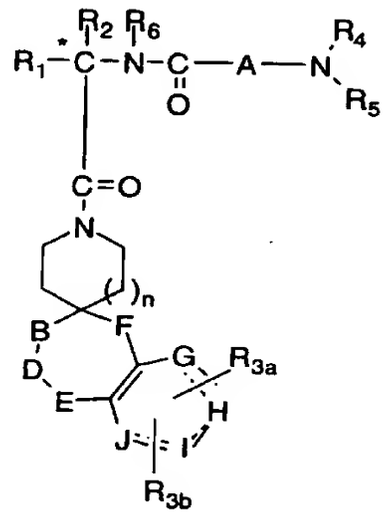


wherein the various substituents are as defined in U.S. Patent 5,283,241 and PCT Patent Publication No. 94/05634.

A representative third class of growth hormone secretagogues is disclosed in PCT Patent Pub. No. WO 94/13696 as compounds of the following structural Formulas I and II:



Formula I



Formula II

wherein:

R_1 is selected from the group consisting of:

$-C_1$-C_{10} alkyl, -aryl, -aryl-(C_1-C_6 alkyl),

$-C_3$-C_7 cycloalkyl-(C_1-C_6alkyl), $-C_1$-C_5alkyl-K-C_1-C_5 alkyl, -aryl(C_0-C_5alkyl)-K-(C_1-C_5 alkyl),

$-C_3$-C_7 cycloalkyl(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl),

wherein K is O, $S(O)_m$, $N(R_2)C(O)$, $C(O)N(R_2)$, OC(O), C(O)O, or $-CR_2=CR_2-$, or $-C\equiv C-$,

and wherein the aryl groups are as defined below and the R_2 and alkyl groups may be futher substituted by 1 to 9 halogen, $S(O)mR_{2a}$, 1 to 3 OR_{2a}, or $C(O)OR_{2a}$, and the aryl groups may be further substituted by phenyl, phenoxy, halophenyl, 1-3 C_1-C_6 alkyl, 1 to 3 halogen, 1 to 2 $-OR_2$, methylenedioxy, $-S(O)_mR_2$, 1 to 2 $-CF_3$, $-OCF_3$, nitro,

-N(R_2)(R_2), -N(R_2)C(O)R_2, -C(O)OR_2, -C(O)N(R_2)(R_2), -SO$_2$N(R_2)(R_2), -N(R_2)S(O)$_2$ aryl, and -N(R_2)SO$_2$$R_2$;

R_2 is selected from the group consisting of: hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_3-C_8 cyclic ring optionally including oxygen, sulfur or NR_{2a};

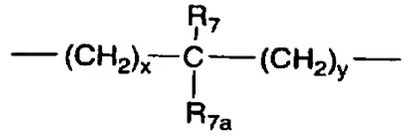
R_{2a} is hydrogen, or C_1-C_6 alkyl;

R_{3a} and R_{3b} are independently selected from the group consisting of: hydrogen, halogen, -C_1-C_6 alkyl, -OR_2, cyano, -OCF$_3$, methylenedioxy, nitro, -S(O)$_m$R, -CF$_3$ or -C(O)OR_2 and when R_{3a} and R_{3b} are in an ortho arrangement, they may be joined to form a C_5 to C_8 aliphatic or aromatic ring optionally including 1 or 2 heteroatoms selected from oxygen, sulfur or nitrogen;

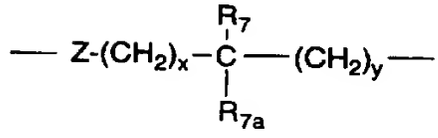
R_4 and R_5 are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, substituted C_1-C_6 alkyl wherein the substituents are selected from 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy, 2-furyl, C_1-C_6 alkoxycarbonyl, -S(O)$_m$(C_1-C_6 alkyl); or R_4 and R_5 can be taken together to form -(CH$_2$)$_r$$L_a$ (CH$_2$)$_s$- where L_a is -C(R_2)$_2$-, -O-, -S(O)$_m$-, or -N(R_2)-, where r and s are independently 1 to 3 and R_2 is as defined above;

R_6 is hydrogen or C_1-C_6 alkyl;

A is:



or



wherein x and y are independently 0-3;
Z is N-R_2 or O;

R_7 and R_{7a} are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, -OR_2, trifluoromethyl, phenyl, substituted C_1-C_6 alkyl where the substituents are selected from imidazolyl, phenyl, indolyl, p-hydroxyphenyl, -OR_2, 1 to 3 fluoro, -$S(O)_mR_2$, -$C(O)OR_2$, -C_3-C_7 cycloalkyl, -$N(R_2)(R_2)$, -$C(O)N(R_2)(R_2)$; or R_7 and R_{7a} can independently be joined to one or both of R_4 and R_5 groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms;

B, D, E, and F are independently selected from the group consisting of: -$C(R_8)(R_{10})$-, -O-, C=O, -$S(O)_m$-, or -NR_9-, such that one or two of B, D, E, or F may be optionally absent to provide a 5, 6, or 7 membered ring; and provided that B, D, E and F can be -$C(R_8)(R_{10})$- or C=O only when one of the remaining B, D, E and F groups is simultaneously -O-, -$S(O)_m$-, or -NR_9-, or

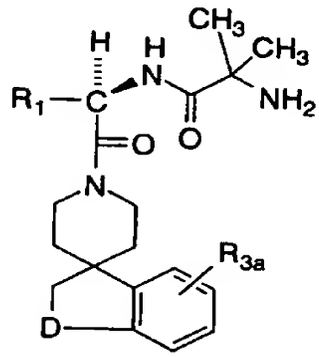
B and D, or D and E taken together may be -$N=CR_{10}$- or -$CR_{10}=N$-, or B and D, or D and E taken together may be -$CR_8=CR_{10}$-, provided one of the other of B and E or F is simultaneously -O-, -$S(O)_m$-, or -NR_9-;

R_8 and R_{10} are independently selected from the group consisting of: hydrogen, -R_2, -OR_2, (-CH_2)$_q$-aryl, -(CH_2)$_q$-C(O)OR_2, -(CH_2)$_q$-C(O)O(CH_2)$_q$-aryl, or -(CH_2)$_q$-(1H-tetrazol-5-yl), where the aryl may be optionally substituted by 1 to 3 halo, 1 to 2 C_1-C_8 alkyl, 1 to 3 -OR_2 or 1 to 2 -C(O)OR_2;

R_9 is selected from the group consisting of:
-R_2, -(CH_2)$_q$-aryl, -C(O)R_2, -C(O)(CH_2)$_q$-aryl, -SO_2R_2, -SO_2(CH_2)$_q$-aryl, -C(O)N(R_2)(R_2), -C(O)N(R_2)(CH_2)$_q$-aryl, -C(O)OR_2, 1-H-tetrazol-5-yl, -SO_3H, -SO_2NHC≡N, -SO_2N(R_2)aryl, -SO_2N(R_2)(R_2),
and wherein the (CH_2)$_q$ may be optionally substituted by 1 to 2 C_1-C_4 alkyl, and the R_2 and aryl may be optionally further substituted by 1 to 3 -OR_{2a}, -O(CH_2)$_q$ aryl, 1 to 2 -C(O)OR_{2a}, 1 to 2 -C(O)O(CH_2)$_q$ aryl, 1 to 2 -C(O)N(R_{2a})(R_{2a}), 1 to 2 -C(O)N(R_{2a})(CH_2)$_q$ aryl, 1 to 5 halogen, 1 to 3 C_1-C_4 alkyl, 1,2,4-triazolyl, 1-H-tetrazol-5-yl, -C(O)NHSO_2R_{2a}, -S(O)$_m$$R_{2a}$, -C(O)N$HSO_2$($CH_2$)q-aryl, -$SO_2$NHC≡N, -$SO_2$NHC(O)$R_{2a}$, -$SO_2$NHC(O)($CH_2$)$_q$aryl, -N($R_2$)C(O)N($R_{2a}$)($R_{2a}$), -N($R_{2a}$)C(O)N($R_{2a}$)($CH_2$)$_q$-aryl, -N($R_{2a}$)($R_{2a}$), -N($R_{2a}$)C(O)$R_{2a}$, -N($R_{2a}$)C(O)($CH_2$)q aryl, -OC(O)N($R_{2a}$)($R_{2a}$), -OC(O)N($R_{2a}$)($CH_2$)$_q$ aryl, -SO_2(CH_2)$_q$CONH-(CH_2)wNHC(O)R_{11},
wherein w is 2-6 and R_{11} may be biotin, aryl, or aryl substituted by 1 or 2 OR_2, 1-2 halogen, azido or nitro;

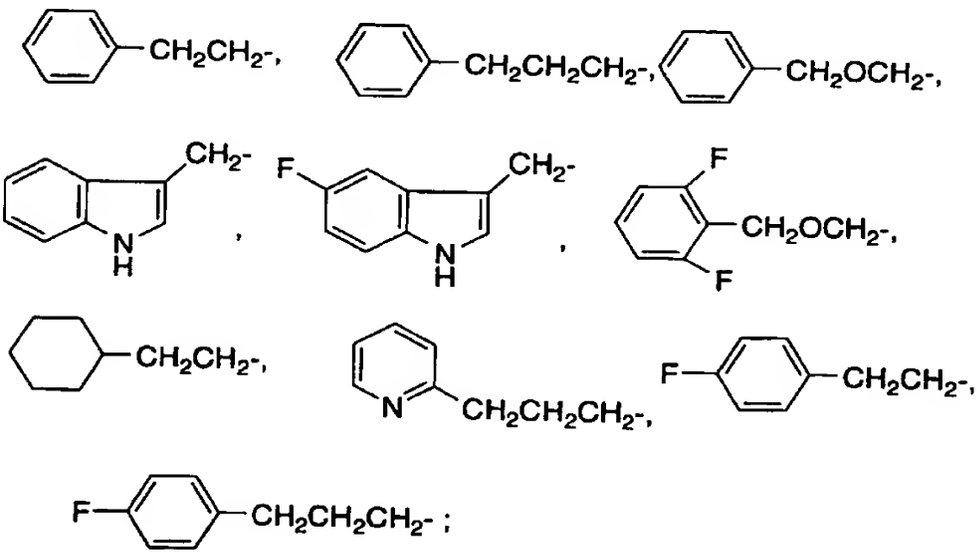
m is 0, 1 or 2;
n is 1, or 2;
q may optionally be 0, 1, 2, 3, or 4; and
G, H, I and J are carbon, nitrogen, sulfur or oxygen atoms, such that at least one is a heteroatom and one of G, H, I or J may be optionally missing to afford a 5 or 6 membered heterocyclic aromatic ring;
and pharmaceutically acceptable salts and individual diastereomers thereof.

Within this third class, the most preferred growth hormone secretagogues employed in the instant invention are realized in structural Formula V:



V

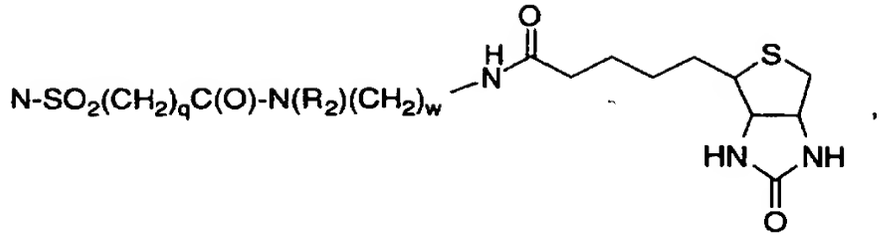
wherein R_1 is selected from the group consisting of:

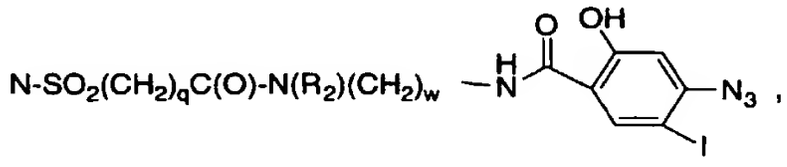


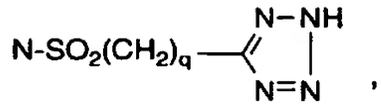
R_{3a} is H, or fluoro;

D is is selected from the group consisting of:

-O-, -S-, -S(O)m-, N(R2), $NSO_2(R_2)$, $NSO_2(CH_2)$taryl, $NC(O)(R_2)$, $NSO_2(CH_2)$qOH, $NSO_2(CH_2)$qCOOR2, $NSO_2(CH_2)$qC(O)-N(R2)(R2), N-$SO_2(CH_2)$qC(O)-N(R2)(CH_2)wOH,







and the aryl is phenyl or pyridyl and the phenyl may be substituted by 1-2 halogen;

R_2 is H, or C_1-C_4 alkyl;
m is 1, 2;
t is 0, 1, or 2;
q is 1, 2, or 3;
w is 2, 3, 4, 5, or 6;
and the pharmaceutically acceptable salts and individual diastereomers thereof.

Representative most preferred growth hormone secretagoues within this third class which may be employed in the present invention include the following:

1) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

2) N-[1(R)-[(1,2-Dihydro-1-methanecarbonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

3) N-[1(R)-[(1,2-Dihydro-1-benzenesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

4) N-[1(R)-[(3,4-Dihydro-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl) carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

5) N-[1(R)-[(2-Acetyl-1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

6) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

7) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide methanesulfonate;

8) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

9) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

10) N-[1(S)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethylthio)ethyl]-2-amino-2-methylpropanamide;

11) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide;

12) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methyl-propanamide;

13) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-4-phenylbutyl]-2-amino-2-methyl-propanamide;

14) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

15) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

16) N-[1(R)-[(1,2-Dihydro-1-(2-ethoxycarbonyl)methylsulfonylspiro-[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

17) N-[1(R)-[(1,2-Dihydro-1,1-dioxospiro[3H-benzothiophene-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

and pharmaceutically acceptable salts thereof.

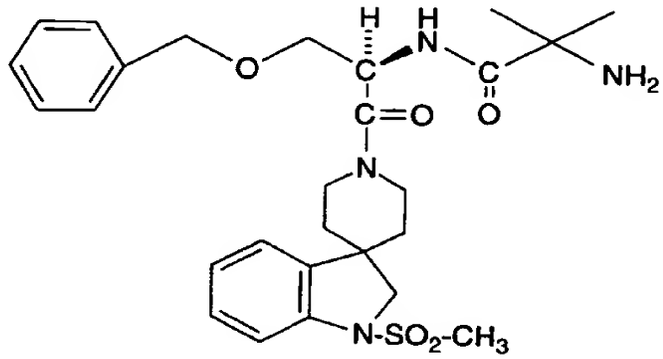
Expecially preferred growth hormone secretagogues within this third class which may be employed in the present invention include:

N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide methanesulfonate;

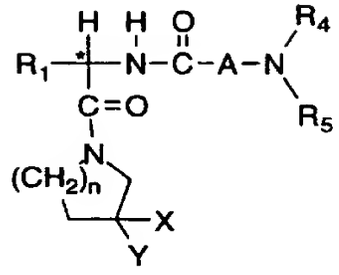
and pharmaceutically acceptable salts thereof.

The most preferred compounds within this third class which may be employed in the present invention are identified as having the following structure:



and pharmaceutically acceptable salts thereof, in particular, the methanesulfonate salt.

A representative fourth class of growth hormone secretagogues is disclosed in U.S. Patent No. 5,492,916 as being compounds of the structural formula I:



Formula I

wherein the various substituents are as defined in U.S. Patent 5,492,916.

In the above structural formulas and throughout the instant specification, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration which may optionally contain double or triple bonds. Exemplary of such alkyl groups are methyl, ethyl, propyl, ethinyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, allyl, propenyl, butenyl, butadienyl and the like. The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration which may optionally contain double or triple bonds. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy allyloxy, propinyloxy, isobutenyloxy, 2-hexenyloxy, and the like. The term "halogen" is intended to include the halogen atom fluorine, chlorine, bromine and iodine. The term "aryl" is intended to include phenyl and naphthyl and aromatic residues of 5- and 6- membered rings with 1 to 3 heteroatoms or fused 5 or 6 membered bicyclic rings with 1 to 3 heteroatoms of nitrogen, sulfur or oxygen. Examples of such heterocyclic aromatic rings are pyridine, thiophene, benzothiophene, tetrazole, indole, N-methylindole, dihydroindole, indazole, N-formylindole, benzimidazole, thiazole, furan, pyrimidine, and thiadiazole.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other. Similarly, the use of a particular variable within a noted structural formula is intended to be independent of the use of such variable within a different structural formula.

For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts." Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include the following: Acetate, Benzenesulfonate, Benzoate, Bicarbonate, Bisulfate, Bitartrate, Borate, Bromide, Calcium, Camsylate, Carbonate, Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluceptate, Gluconate, Glutamate, Glycollylarsanilate, Hexylresorcinate, Hydrabamine, Hydrobromide, Hydrochloride, Hydroxynaphthoate, Iodide, Isothionate, Lactate, Lactobionate, Laurate, Malate, Maleate, Mandelate, Mesylate, Methylbromide, Methylnitrate, Methylsulfate, Mucate, Napsylate, Nitrate, N-methylglucamine ammonium salt, Oleate, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Salicylate, Stearate, Subacetate, Succinate, Sulfate, Sulfonate, Tannate, Tartrate, Teoclate, Tosylate, Triethiodide and Valerate. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts.

The compounds employed in the present invention, may have chiral centers and occur as racemates, racemic mixtures and as individual diastereomers, or enantiomers with all isomeric forms being included in the present invention. Therefore, where a compound is chiral,

the separate enantiomers, substantially free of the other, are included within the scope of the invention; further included are all mixtures of the two enantiomers.

Full descriptions of the preparation of the growth hormone secretagoue employed in the present invention may be found e.g., in: U.S. Patent No. 3,239,345; U.S. Patent No. 4,036,979; U.S. Patent No. 4,411,890; U.S. Patent No. 5,206,235; U.S. Patent No. 5,283,241; U.S. Patent No. 5,284,841; U.S. Patent No. 5,310,737; U.S. Patent No. 5,317,017; U.S. Patent No. 5,374,721; U.S. Patent No. 5,430,144; U.S. Patent No. 5,434,261; U.S. Patent No. 5,438,136; U.S. Patent No. 5,494,919; U.S. Patent No. 5,494,920; U.S. Patent No. 5,492,916; U.S. Patent No. 5,536,716; EPO Patent Pub. No. 0,144,230; EPO Patent Pub. No. 0,513,974; PCT Patent Pub. No. WO 89/07110; PCT Patent Pub. No. WO 89/07111; PCT Patent Pub. No. WO 93/04081; PCT Patent Pub. No. WO 94/07486; PCT Patent Pub. No. WO 94/08583; PCT Patent Pub. No. WO 94/11012; PCT Patent Pub. No. WO 94/13696; PCT Patent Pub. No. WO 94/19367; PCT Patent Pub. No. WO 95/03289; PCT Patent Pub. No. WO 95/03290; PCT Patent Pub. No. WO 95/09633; PCT Patent Pub. No. WO 95/11029; PCT Patent Pub. No. WO 95/12598; PCT Patent Pub. No. WO 95/13069; PCT Patent Pub. No. WO 95/14666; PCT Patent Pub. No. WO 95/16675; PCT Patent Pub. No. WO 95/16692; PCT Patent Pub. No. WO 95/17422; PCT Patent Pub. No. WO 95/17423; PCT Patent Pub. No. WO 95/34311; PCT Patent Pub. No. WO 96/02530; PCT Patent Pub. No. WO 96/05195; PCT Patent Pub. No. WO 96/15148; PCT Patent Pub. No. WO 96/22782; PCT Patent Pub. No. WO 96/22997; PCT Patent Pub. No. WO 96/24580; PCT Patent Pub. No. WO 96/24587; PCT Patent Pub. No. WO 96/35713; PCT Patent Pub. No. WO 96/38471; PCT Patent Pub. No. WO 97/00894; PCT Patent Pub. No. WO 97/06803; PCT Patent Pub. No. WO 97/07117; J. Endocrinol Invest., 15(Suppl 4), 45 (1992)); Science, 260, 1640-1643 (June 11, 1993); Ann. Rep. Med. Chem., 28, 177-186 (1993); Bioorg. Med. Chem. Ltrs., 4(22), 2709-2714 (1994); and Proc. Natl. Acad. Sci. USA 92, 7001-7005 (July 1995), as well as herein.

Methods to obtain the growth hormone releasing peptides GHRP-6 and GHRP-1 are described in U.S. Patent Nos. 4,411,890 and

PCT Patent Publications WO 89/07110, WO 89/07111, methods to obtain the growth hormone releasing peptide GHRP-2 are described in PCT Patent Publication WO 93/04081, and methods to obtain hexarelin are described in J. Endocrinol Invest., 15(Suppl 4), 45 (1992).

The identification of a compound as a growth hormone secretagogue and thus able to directly or indirectly stimulate or increase the endogenous release of growth hormone in an animal may be readily determined without undue experimentation by methodology well known in the art, such as the assay described by Smith, *et al.*, *Science*, *260*, 1640-1643 (1993) (see text of Figure 2 therein). In a typical experiment pituitary glands are aseptically removed from 150-200 g Wistar male rats and cultures of pituitary cells are prepared according to Cheng et al. *Endocrinol.* , *124*, 2791-2798 (1989). The cells are treated with the subject compound and assayed for growth hormone secreting activity and intracellular cAMP levels as described by Chang et al. In particular, the intrinsic growth horomone secretagogue activity of a compounds which may be used in the present invention may be determined by this assay.

The term "therapeutically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician.

Accordingly, the present invention includes within its scope the use of a growth hormone secretagogue, alone or in combination with other agents, for the prevention or treatment of sleep disorders and sleep disturbances in a warm-blooded animal. For the purposes of this disclosure, a warm-blooded animal is a member of the animal kingdom which includes but is not limited to mammals and birds. The preferred mammal for purposes of this invention is human.

Included within the scope of the present invention is the method of using a growth hormone secretagogue for enhancing and improving the quality of sleep. The growth hormone secretagogue is useful in enhancing or improving sleep quality as well as preventing and treating sleep disorders and sleep disturbances in a warm-blooded animal. In addition, the use of the growth hormone secretagogue increases sleep

efficiency and augments sleep maintenance. The growth hormone secretagogue may further be used in a a method for preventing and treating sleep disorders and sleep disturbances in a warm-blooded animal. The present invention further provides a pharmaceutical composition for enhancing or improving sleep quality and increasing sleep efficiency and sleep maintenance.

The present method of using a growth hormone secretagogue further provides the following: an increase in the value which is calculated from the time that a subject sleeps divided by the time that a subject is attempting to sleep; a decrease in sleep latency (the time it takes to fall asleep); a decrease in difficulties in falling asleap; a decrease in the number of awakenings during sleep; a decrease in nocturnal arousals; a decrease in the time spent awake following the initial onset of sleep; an increase in the total amount of sleep; an increase the amount and percentage of REM sleep; an increase in the duration and occurrence of REM sleep; a reduction in the fragmentation of REM sleep; an increase in the amount and percentage of slow-wave (i.e. stage 3 or 4) sleep; an increase in the amount and percentage of stage 2 sleep; an enhancement of EEG-delta activity during sleep; a decrease in the number of awakenings; a decrease in nocturnal arousals, especially early morning awakenings; an increase in daytime alertness; an increased satisfaction with the intensity of sleep; and increased sleep maintenance. Secondary outcomes which may be provided by the present invention include enhanced cognitive function and increased memory retention.

The present invention is further useful for the prevention and treatment of sleep disorders and sleep disturbances including: sleep problems associated with insomnia, hypersomnia, sleep apnea, narcolepsy, nocturnal myoclonus, REM sleep interruptions, jet-lag, shift workers' sleep disturbances, dysomnias, night terror, insomnias associated with depression or with emotional/mood disorders, as well as sleep walking and enuresis, as well as sleep disorders which accompany aging, conditions associated with circadian rhythmicity, mental and physical disorders associated with travel across time zones and with rotating shift-work schedules, or syndromes such as fibromyalgia which are manifested

by non-restorative sleep and muscle pain or sleep apnea which is associated with respiratory disturbances during sleep.

This particular application of growth hormone secretagogues provides unexpected benefit relative to the administration of exogenous growth hormone. In particular, the growth hormone secretagogue enhances the normal pulsatile releases of endogenous growth hormone or growth hormone-releasing hormone and thus is more likely to reproduce the natural pattern of endogenous growth hormone release, especially with regard to increasing the level of endogenous growth hormone prior to or in during the initial onset of sleep. Growth hormone secregagogues which are orally active also have the benefit being able to be administered orally, rather than just intravenously, intraperitoneally or subcutaneously. Although the specific mechanism underlying the present invention is not currently understood, it may be possible that the growth hormone secretagogue not only stimulates the production of growth hormone which provides benefical outcomes in sleep, but it also acts to increase the levels of growth hormone-releasing hormone and/or somatostatin which then directly enhance the quality of sleep.

In addition, the present invention includes within its scope a pharmaceutical composition for enhancing and improving the quality of sleep comprising, as an active ingredient, at least one growth hormone secretagogues in association with a pharmaceutical carrier or diluent. Optionally, the active ingredient of the pharmaceutical compositions can comprise an anabolic agent in addition to at least one growth hormone secretagogue or another composition which exhibits a different activity, e.g., an antibiotic growth promoting agent or in combination with a corticosteroid to minimize the catabolic side effects or with other pharmaceutically active materials wherein the combination enhances efficacy and minimizes side effects. Growth promoting and anabolic agents include, but are not limited to, TRH, diethylstilbesterol, estrogens, β-agonists, theophylline, anabolic steroids, dehydroepiandrosterone, enkephalins, E series prostaglandins, retinoic acid, compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeranol, and compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox. or peptides disclosed in U.S.

Patent No. 4,411,890. Similarly, the growth hormone secretagogue may be administered with somatomedin-C for the treatment of disorders characterized by non-restorative sleep, such as fibromyalgia (U.S. Patent No. 5,378,686).

The present invention further includes the use of a growth hormone secretagogue in the manufacture of a medicament for enhancing and improving the quality of sleep and for the treatement of sleep disorders and sleep disturbances.

In addition, the present invention contemplates the use of a growth hormone secretagogue for enhancing and improving the quality of sleep in combination with another growth hormone secretagogues such as those referenced herein, including the growth hormone releasing peptides GHRP-6 and GHRP-1 (described in U.S. Patent No. 4,411,890 and PCT publications WO 89/07110, WO 89/07111) and GHRP-2 (described in WO 93/04081) and B-HT920, as well as hexarelin or growth hormone releasing hormone (GHRH, also designated GRF) and its analogs, or growth hormone and its analogs, or somatomedins including IGF-1 and IGF-2, or with α-adrenergic agonists such as clonidine or serotonin 5HTD agonists such as sumatriptan, or agents which inhibit somatostatin or its release such as physostigmine and pyridostigmine. For example, a growth hormone secretagogue may be used in combination with IGF-1 for enhancing and improving the quality of sleep.

It will be known to those skilled in the art that there are numerous compounds now being used in an effort to enhance and improve the quality of sleep. Combinations of these therapeutic agents some of which have also been mentioned herein with a growth hormone secretagogue will bring additional, complementary, and often synergistic properties to enhance the desirable properties of these various therapeutic agents. In these combinations, the growth hormone secretagogue and the therapeutic agents may be independently present in dose ranges from one one-hundredth to one times the dose levels which are effective when these compounds and secretagogues are used singly.

The growth hormone secretagogue may be administered in combination with sedatives, hypnotics, anxiolytics, antipsychotics,

antianxiety agents, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents, benzodiazepines, barbituates, 5HT-2 antagonists, and the like, or the growth hormone secretagogue may be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation. For example, to enhance and improve the quality of sleep a growth hormone secretagogue may be given in combination with such compounds as: adinazolam, allobarbital, alonimid, alprazolam, amitriptyline, amobarbital, amoxapine, bentazepam, benzoctamine, brotizolam, bupropion, busprione, butabarbital, butalbital, capuride, carbocloral, chloral betaine, chloral hydrate, chlordiazepoxide, clomipramine, cloperidone, clorazepate, clorethate, clozapine, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, estazolam, ethchlorvynol, etomidate, fenobam, flunitrazepam, flurazepam, fluvoxamine, fluoxetine, fosazepam, glutethimide, halazepam, hydroxyzine, imipramine, lithium, lorazepam, lormetazepam, maprotiline, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, midaflur, midazolam, nefazodone, nisobamate, nitrazepam, nortriptyline, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, reclazepam, roletamide, secobarbital, sertraline, suproclone, temazepam, thioridazine, tracazolate, tranylcypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, zolazepam, zolpidem, and salts thereof, and combinations thereof, and the like, as well as admixtures and combinations thereof.

Typically, the individual daily dosages for these combinations may range from about one-fifth of the minimally recommended clinical dosages to the maximum recommended levels for the entities when they are given singly.

To illustrate these combinations, a growth hormone secretagogue effective clinically effective clinically at a given daily dose range may be effectively combined, at levels which are equal or less than

the daily dose range, with the following compounds at the indicated per day dose range: adinazolam, allobarbital, alonimid, alprazolam, amitriptyline, amobarbital, amoxapine, bentazepam, benzoctamine, brotizolam, bupropion, busprione, butabarbital, butalbital, capuride, carbocloral, chloral betaine, chloral hydrate, chlordiazepoxide, clomipramine, cloperidone, clorazepate, clorethate, clozapine, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, estazolam, ethchlorvynol, etomidate, fenobam, flunitrazepam, flurazepam, fluvoxamine, fluoxetine, fosazepam, glutethimide, halazepam, hydroxyzine, imipramine, lithium, lorazepam, lormetazepam, maprotiline, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, midaflur, midazolam, nefazodone, nisobamate, nitrazepam, nortriptyline, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, reclazepam, roletamide, secobarbital, sertraline, suproclone, temazepam, thioridazine, tracazolate, tranylcypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, zolazepam, zolpidem, and salts thereof, and combinations thereof, and the like, as well as admixtures and combinations thereof. It will be readily apparent to one skilled in the art that the growth hormone secretagogue may be employed with other agents to control sleep disorders and sleep disturbances in depressed patients and/or provide benefit in the prevention or treatment of sleep disorders and sleep disturbances.

Naturally, these dose ranges may be adjusted on a unit basis as necessary to permit divided daily dosage and, as noted above, the dose will vary depending on the nature and severity of the disease, weight of patient, special diets and other factors.

Anabolic effects especially in the treatment of geriatric male patients are obtained with compounds of this invention in combination with anabolic steroids such as dehydroepiandrosterone, oxymetholone, methyltesterone, fluoxymesterone, restosterone and stanozolol.

These combinations may be formulated into pharmaceutical compositions as known in the art and as discussed below. A growth hormone secretagogue may be administered alone or in combination by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual, or topical routes of administration and can be formulated in dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. Illustrative of the adjuvants which may be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent such as corn starch, pregelatinized starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. When the dosage unitform is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. Tablets and pills can additionally be prepared with enteric coatings and tablets may be coated with shellac, sugar or both.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and

propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Sterile compositions for injection may be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or a synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, antioxidants and the like may be incorporated as required. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax. Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

The dosage of active ingredient in the compositions of this invention may be varied, however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The active ingredient may be administered to patients (animals and human) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. The dose will vary from patient to patient depending upon the nature and severity of disease, the patient's weight, special diets

then being followed by a patient, concurrent medication, and other factors which those skilled in the art will recognize. Generally, dosage levels of between 0.0001 to 10 mg/kg. of body weight daily are administered to patients and animals, e.g., mammals, to obtain effective release of growth hormone. The dosage range will generally be about 0.5 mg to 1.0 g. per patient per day which may be administered in single or multiple doses. Perferably, the dosage range will be about 0.5 mg to 500 mg per patient per day; more preferably about 0.5 mg to 200 mg per patient per day; and even more preferably about 5 mg to 50 mg per patient per day.

Pharmaceutical compositions of the present invention may be provided in a solid dosage formulation preferably comprising about 0.5 mg to 500 mg active ingredient, more preferably comprising about 1 mg to 250 mg active ingredient. The pharmaceutical composition is preferably provided in a solid dosage formulation comprising about 1 mg, 5 mg, 10 mg, 25 mg, 50 mg, 100 mg, 200 mg or 250 mg active ingredient.

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

EXAMPLE 1

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide,

Step A: 3-Amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

A solution of 9.22 g (45.6 mmol) of 3-azido-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (prepared by the method of Watthey, et al., J. Med. Chem., 28, 1511-1516 (1985)) in 30 mL methanol was hydrogenated at 40 psi in the presence of 1.0 g of 5% Pt/C for 4.5 hours. Celite was added and the mixture filtered through a pad of Celite. The filtrate was concentrated and allowed to stand for 16 hours at room temperature which resulted in formation of crystals. The material was isolated by filtration and dried under vacuum to afford 4.18 g (23.7

mmol, 52%) of the product. The mother liquors were diluted to 100 mL with methanol, treated with 2 g of charcoal, filtered through Celite and the filtrate concentrated under vacuum to approximatley 15 mL. A second crop formed yielding 2.02 g of product (11.5 mmol, 25%). Another recycling of the mother liquors afforded a third crop of 0.88 g (5.0, 11%). A total of 7.08 g (40.2 mmol, 88%) of the product was thus obtained. ^{1}H NMR (200 MHz, $CDCl_3$): 1.6 (br s, 2H), 1.80 (m, 1H), 2.55 (m, 2H), 2.88 (m, 1H), 3.42 (dd; 7Hz, 11Hz; 1H), 6.98 (d, 8Hz, 1H), 7.2 (m, 3H), 8.3 (br s, 1H). FAB-MS: calculated for $C_{10}H_{12}N_2O$ 176; found 177 (M+H, 100%).

Step B: 3(R)-Amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

2.37 g (13.5 mmol) of 3-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Step A) and 2.02 g (13.5 mmol) of L-tartaric acid were suspended in 40 mL of ethanol. The mixture was gently heated and complete dissolution achieved by dropwise addition of 5 mL of distilled water. The solution was cooled to room temperature and aged overnight. The solid that formed was removed by filtration, washed with ethanol/diethyl ether (1:1) and dried under vacuum to afford 1.75 g of crude L-tartrate salt. The mother liquors were evaporated to dryness under vacuum, redissolved in 40 mL of water and the pH adjusted to 10-11 by the addition of solid potassium carbonate. The mixture was extracted with chloroform (6x20 mL) and the combined extracts washed with water (1x) and brine (1x), dried over potassium carbonate, filtered and solvents removed under vacuum to afford 1.29 g (7.33 mmol) of partially enriched 3(R) amine. The original 1.75 g batch of L-tartrate salt was recrystallized twice from aqueous ethanol to afford 1.03 g (3.17 mmol, 24%) of purified L-tartrate salt with $[a]_D=-212°$ (c=1, H_2O). The purified L-tartrate salt was dissolved in 20 mL of water and the pH adjusted to 10-11 by the addition of solid potassium carbonate. The mixture was extracted with chloroform (5x10 mL); combined extracts were washed with water and brine then dried over potassium carbonate, filtered and solvents removed under vacuum to afford 522 mg (2.96 mmol, 22% overall) of the 3(S) amine, $[a]_D=-446°$ (c=1,CH_3OH). The

remaining 1.29 g (7.33 mmol) of partially enriched 3(R) amine was treated with 1.10 g (7.33 mmol) of D-tartaric acid as described above and the resulting salt recrystallized twice from aqueous ethanol to afford 1.20 g of purified D-tartrate salt, $[a]_D=-214°$ (c=1,H_2O). The purified D-tartrate salt was dissolved in 20 mL of water and the free base isolated as described above to give 629 mg (3.57 mmol, 26% overall) of the 3(R) amine, $[a]_D=+455°$ (c=1,CH_3OH).

Step C: 2,2-Dimethylbutanedioic acid, 4-methyl ester

2,2-dimethylsuccinic acid (20 g, 137 mmol) dissolved in 200 mL absolute methanol at 0°C was treated dropwise with 2 mL concentrated sulfuric acid. After the addition was complete, the mixture was allowed to warm to room temperature and stirred for 16 hours. The mixture was concentrated *in vacuo* to 50 mL and slowly treated with 200 mL of saturated aqueous sodium bicarbonate. The mixture was washed with hexane (3x) and the aqueous layer removed and cooled in an ice bath. The mixture was acidified to pH 2 by slow addition of 6N HCl then extracted with ether (8x). The combined extracts were washed with brine, dried over magnesium sulfate, filtered and solvents removed *in vacuo*. The residue was dried at room temperature under vacuum to afford 14.7 g (91.8 mmol, 67%) of a viscous oil that slowly solidified upon standing. ^1H NMR analysis indicates the product is a mixture of the title compound and 15% of the isomeric 2,2-dimethylbutanedioic acid, 1-methyl ester. NMR (200 MHz, $CDCl_3$) of title compound: 1.29 (s, 6H), 2.60 (s, 2H), 3.66 (s, 3H). NMR (200 MHz, $CDCl_3$) of isomer: 1.28 (s, 6H), 2.63 (s, 2H), 3.68 (s, 3H).

Step D: 3-[Benzyloxycarbonylamino]-3-methylbutanoic acid, methyl ester

To 14.7 g (91.8 mmol) of 2,2-dimethylbutanedioic acid-4-methyl ester (Step C), containing 15% of the isomeric 1-methyl ester compound, in 150 mL benzene was added 13 mL of triethylamine (9.4 g, 93 mmol, 1.01 eq) followed by 21.8 mL diphenylphosphoryl azide (27.8 g, 101 mmol, 1.1 eq). The mixture was heated under nitrogen at reflux

for 45 minutes then 19 mL (19.9 g, 184 mmol, 2 eq) of benzyl alcohol was added and refluxing continued for 16 hours. The mixture was cooled, filtered and the filtrate concentrated to a minimum volume under vacuum. The residue was redissolved in 250 mL ethyl acetate, washed with water (1x), saturated aqueous sodium bicarbonate (2x) and brine (1x). The organic layer was removed, dried over magnesium sulfate, filtered and the filtrate concentrated to a minimum volume *in vacuo*. The crude product was purified by medium pressure liquid chromatography on silica, eluting with hexane/ethyl acetate (4:1), to afford 18.27 g (68.9 mmol, 75%) of the title compound as a pale yellow liquid in addition to a small amount of pure 3-[benzyloxycarbonylamino]-2,2-imethylpropanoic acid, methyl ester. ^{1}H NMR (200MHz, $CDCl_3$) of title compound: 1.40 (s, 6H), 2.69 (s, 2H), 3.63 (s, 3H), 5.05 (s, 2H), 5.22 (br s, 1H), 7.32 (s, 5H). ^{1}H NMR (200 MHz, $CDCl_3$) of 3-[benzyloxycarbonylamino]-2,2-dimethylpropanoic acid, methyl ester (200 MHz, $CDCl_3$): 1.19 (s, 6H), 3.30 (d, 7Hz, 2H; resonance collapses to singlet in CD_3OD), 3.67 (s, 3H), 5.09 (s, 2H), 5.22 (br s,1H; resonance not observed in CD_3OD), 7.3 (br s, 5H).

Step E: 3-Benzyloxycarbonylamino-3-methylbutanoic acid

A solution of 18.27 g (68.9 mmol) of methyl 3-benzyloxycarbonylamino-3-methylbutanoate (Step D) in 20 mL of methanol at room temperature was treated dropwise with 51 mL of 2N NaOH (102 mmol, 1.5 eq). The mixture was stirred at room temperature for 16 hours then transferred to a separatory funnel and washed with hexane (3x). The aqueous layer was removed, cooled to 0°C and slowly acidified to pH 2 (paper) by dropwise addition of 6N HCl. This mixture was extracted with ether (6x); combined extracts were washed with 1N HCl and brine, then dried over magnesium sulfate, filtered and solvent removed under vacuum to afford 17.26 g (68.7 mmol, 99%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 1.42 (s, 6H), 2.77 (s, 2H), 5.06 (s, 2H), 5.2 (br s, 1H), 7.3 (s, 5H).

Step F: 3-Benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide

To a solution of 252 mg (1.43 mmol) of 3(R)-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (Step B) in 4 mL of methylene chloride at room temperature was added 400 mg (1.60 mmol, 1.1 eq) of 3-benzyloxycarbonylamino-3-methylbutanoic acid (Step E) followed by 760 mg (1.7 mmol, 1.2 eq) benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluoro-phosphate and 0.50 mL of diisopropyl-ethylamine (380 mg, 2.9 mmol, 2 eq). After 3 hours at room temperature, the mixture was diluted into 30 mL of ethyl acetate and washed with 5% aqueous citric acid, saturated aqueous sodium bicarbonate (2x) and brine. The organic layer was removed, dried over magnesium sulfate, filtered and solvents removed under vacuum. The residue was purified by medium pressure liquid chromatography on silica, eluting with ethyl acetate to afford 586 mg (1.43 mmol, 100%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 1.38 (s, 3H), 1.39 (s, 3H), 1.82 (m, 1H), 2.52 (s, 2H), 2.5-3.0 (m, 3H), 4.51 (m, 1H), 5.07 (br s, 2H), 5.57 (br s, 1H), 6.68 (d, 7Hz, 1H), 6.97 (d, 8Hz, 1H), 7.1-7.4 (m, 8H), 7.61 (br s, 1H). FAB-MS: calculated for $C_{23}H_{27}N_3O_4$ 409; found 410 (M+H, 100%); $[a]_D$=+137° (c=1, $CHCl_3$).

Step G: 5-Phenyltetrazole

Zinc chloride (3.3 g, 24.3 mmol, 0.5 eq) was added to 15 mL of N,N-dimethylformamide in small portions while maintaining the temperature below 60°C. The suspension of zinc chloride was cooled to room temperature and treated with 5.0 g of benzonitrile (48.5 mmol, 1.0 eq) followed by 3.2 g of sodium azide (48.5 mmol, 1.0 eq). The heterogeneous mixture was heated at 115°C with agitation for 18 hours. The mixture was cooled to room temperature, water (30 mL) was added and the mixture acidified by the addition of 5.1 mL of concentrated hydrochloric acid. The mixture was cooled to 0°C and aged for one hour, then filtered and the filter cake washed with 15 mL of cold 0.1N HCl then dried at 60°C under vacuum to afford 6.38 g (43.7 mmol, 90%) of the product.

Step H: 5-Phenyl-2-trityltetrazole

To a suspension of 5.0 g (34.2 mmol) of 5-phenyltetrazole in 55 mL of acetone was added 5.0 mL of triethylamine (3.6 g, 35.6 mmol, 1.04 eq). After 15 minutes, a solution of 10.0 g of triphenyl-methyl chloride (35.9 mmol, 1.05 eq) in 20 mL of tetrahydrofuran was added and the mixture stirred at room temperature for one hour. Water (75 mL) was slowly added and the mixture stirred for one hour at room temperature. The product was collected by filtration, washed with 75 mL of water and dried at 60°C under vacuum to give 13.3 g (34.2 mmol, 100%) of the product.

Step I: N-Triphenylmethyl-5-[2-(4'-methylbiphen-4-yl)] tetrazole

A solution of zinc chloride (6.3 g, 46.2 mmol, 0.6 eq) in 35 mL of tetrahydrofuran was dried over molecular sieves. 5-Phenyl-2-trityltetrazole (30.0 g, 77.3 mmol, 1.0 eq) was dissolved in 300 mL of dry tetrahydrofuran and the solution gently stirred while being degassed three times by alternating vacuum and nitrogen purges. The stirred solution was cooled to -15°C and treated slowly with 50.5 mL of 1.6 M n-butyllithium in hexane (80.0 mmol, 1.05 eq) so as to maintain the temperature below -5°C. The solution was maintained at -5 to -15°C for 1.5 hours then treated with the dried zinc chloride solution and allowed to warm to room temperature. In a separate flask, 4-iodotoluene (20.17 g, 92.5 mmol, 1.2 eq) and bis-(triphenylphosphine)nickel (II) dichloride (1.5 g, 2.3 mmol, 0.03 eq) were dissolved in 60 mL of tetrahydrofuran, then degassed and left under an atmosphere of nitrogen. The mixture was cooled to 5°C and treated with 1.5 mL of 3.0 M solution of methylmagnesium chloride in tetrahydrofuran (4.5 mmol, 0.06 eq) so as to keep the temperature below 10°C. The solution was warmed to room temperature and added, under nitrogen purge, to the arylzinc solution. The reaction mixture was stirred vigorously for 8 hours at room temperature then quenched by the slow addition of a solution of 10 mL of glacial acetic acid (1.6 mmol, 0.02 eq) in 60 mL of tetrahydrofuran at a rate so that the temperature was maintained below 40°C. The mixture was stirred for 30 minutes and 150 mL of 80% saturated aqueous sodium

chloride was added; the reaction mixture was extracted for 30 minutes and the layers allowed to separate. The organic layer was removed and washed with 150 mL of 80% saturated aqueous sodium chloride buffered to pH>10 by the addition of ammonium hydroxide. The organic phase was removed and concentrated under vacuum to approximately 50 mL then 250 mL of acetonitrile was added. The mixture was again concentrated under vacuum to 50 mL and acetonitrile added to make the final volume 150 mL. The resulting slurry was cooled at 5°C for 1 hour then filtered and washed with 50 mL of cold acetonitrile followed by 150 mL of distilled water. The filter cake was air dried to a free flowing solid then further dried under vacuum at 50°C for 12 hours to afford 30.0 g (62.8 mmol, 81%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 2.28 (s, 3H), 6.9-7.05 (m, 10H), 7.2-7.5 (m, 12H), 7.9 (m, 1H).

Step J: N-Triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole

A solution of 3.15 g (6.6 mmol) of N-triphenylmethyl-5-[2-(4'-methylbiphen-4-yl)] tetrazole (Step I) in 25 mL of methylene chloride was treated with 1.29 g (7.25 mmol, 1.1 eq) of N-bromo-succinimide, 80 mg (0.5 mmol, 0.07 eq) of AIBN, 200 mg of sodium acetate and 200 mg of acetic acid. The mixture was heated at reflux for 2 to 16 hours then cooled and washed with saturated aqueous sodium bicarbonate. The organic layer was removed, dried over sodium sulfate, filtered and concentrated to a minimum volume by atmospheric distillation. Methyl t-butyl ether was added and distillation continued until almost all the methylene chloride was removed the the total volume reduce to approximately 12 mL and 12 mL of hexanes was then added. The mixture was kept at room temperature for 2 hours and the product isolated by filtration, washed with hexanes then dried under vacuum at 50°C to give 2.81g (5.04 mmol, 76%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 4.38 (s, 2H), 6.9-8.0 (m, 23H). NMR indicates presence of approximately 1% of the starting material and 7% of the dibromo derivative.

Step K: 3-Benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3(R)-yl]-butanamide

To a solution of 437 mg (1.07 mmol) of the intermediate obtained in Step F in 2 mL of dry dimethylformamide at room temperature under nitrogen was added 55 mg of 60% sodium hydride oil dispersion (33 mg NaH, 1.38 mmol, 1.3 eq). After 15 minutes, a solution of 715 mg (1.28 mmol, 1.2 eq) N-triphenyl-methyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole (Step J) in 1.5 mL of dry dimethyl-formamide was added and the mixture stirred for 90 minutes. The reaction mixture was added to 100 mL of ethyl acetate and washed with water (2x) and brine. The organic layer was removed, dried over magnesium sulfate, filtered and solvents removed under vacuum. Purification by medium pressure liquid chromatography on silica, eluting with ethyl acetate/hexane (1:1), afforded 902 mg (1.02 mmol, 95%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 1.38 (s, 3H), 1.39 (s, 3H), 1.68 (m, 1H), 2.2-2.5 (m, 5H), 4.44 (m, 1H), 4.67 (d, 14Hz, 1H), 5.06 (s, 2H), 5.12 (d, 14Hz, 1H), 5.63 (br 1, 1H), 6.65 (d, 8Hz, 1H), 6.9-7.5 (m, 31H), 7.85 (m, 1H).

Step L: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

A solution of 902 mg (1.02 mmol) of the intermediate obtained in Step H in 5 mL methanol was hydrogenated at room temperature and one atmosphere over 160 mg of 20% $Pd(OH)_2/C$ for 14 hours. The mixture was filtered through Celite and concentrated under vacuum. The residue was purified by reverse phase HPLC on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 60% methanol increased to 80% methanol over 10 minutes) to afford 568 mg (0.91 mmol, 89%) of the title compound. ^{1}H NMR (200 MHz, CD_3OD): 1.33 (s, 3H), 1.37 (s, 3H), 2.0-2.6 (m, 6H), 4.35 (dd; 7, 11 Hz; 1H), 4.86 (d, 15 Hz, 1H), 5.20 (d, 15 Hz, 1H), 7.00 (d, 8 Hz, 2H), 7.15-

7.35 (m, 6H), 7.45-7.70 (m, 4H). FAB-MS: calculated for $C_{29}H_{31}N_7O_2$ 509; found 510 (M+H, 100%).

EXAMPLE 2

3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

Step A: 3-[(2-(R)-Benzyloxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate

The title compound was prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate (Example 1) and (R)-2-benzyloxlpropanal (prepared from ethyl-D-lactate according to the procedure of Hanessian and Kloss, Tetrahedron Lett., 26, 1261-1264 (1985) by the procedure described in U.S. Patent No. 5,206,235, Example 86, Step A. ^{1}H NMR (200MHz, CD_3OD): 1.25 (d, 6Hz, 3H), 1.35 (s, 6H), 2.11 (m, 1H), 2.32 (m, 1H), 2.5-2.7 (m, 4H), 2.95 (m, 1H), 3.17 (m, 1H), 3.80 (m, 1H), 4.40 (m, 1H), 4.44 (d, 11Hz, 1H), 4.64 (d, 11Hz, 1H), 4.90 (d, 15Hz, 1H), 5.02 (d, 15Hz, 1H), 6.99 (d, 8Hz, 2H), 7.1-7.7 (m, 15H). FAB-MS: calculated for $C_{39}H_{43}N_7O_3$ 657; found 658 (M+H, 100%).

Step B: 3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step A by the procedure described in U.S. Patent No. 5,206,235, Example 86, Step B. ^{1}H NMR (400MHz, CD_3OD): 1.22 (d, 6Hz, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 2.10 (m, 1H), 2.31 (m, 1H), 2.45-

2.70 (m, 4H), 2.81 (dd; 10, 12Hz; 1H), 3.08 (dd; 4, 12Hz; 1H), 3.92 (m, 1H), 4.36 (dd; 7, 11Hz; 1H), 4.93 (d, 15Hz, 1H), 5.17 (d, 15Hz, 1H), 7.04 (d, 8Hz, 2H), 7.19 (d, 8Hz, 2H), 7.20-7.35 (m, 4H), 7.54 (m, 2H), 7.65 (m, 2H). FAB-MS: calculated for $C_{32}H_{37}N_7O_3$ 567; found 568 (M+H, 45%).

EXAMPLE 3 (METHOD 1)

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide

Step A: 1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdine]hydrochloride

To a solution of 1.20 g (5.8mmol) of 1'-methyl-1,2-dihydro-spiro[3H-indole-3,4'-piperdine] (prepared as described by H. Ong, et al., J. Med. Chem., 23, 981-986 (1983)) in 20 mL of dry dichloromethane at 0°C was added triethylamine (0.90 mL; 6.4 mmol) and methanesulfonyl chloride (0.49 mL; 6.35 mmol) and stirred for 30 min. The reaction mixture was poured into 15 mL of saturated aqueous sodium bicarbonate solution and extracted with dichloromethane (2X10 mL). The combined organics were washed with brine (20 mL), dried over anhydrous potassium carbonate, filtered and the solvent removed under reduced pressure to yield 1.44 g of the methanesulfonamide derivative as pale yellow oil which was used without purification.

To a solution of above crude product in 20 mL of dry 1,2-dichloroethane at 0°C was added 1.0 mL (9.30 mmol) of 1-chloroethyl chloroformate, and then stirred at RT for 30 min and finally at reflux for 1h. The reaction mixture was concentrated to approximately one third of the volume and then diluted with 20 mL of dry methanol and refluxed for 1.5h. The reaction was cooled to RT and concentrated to approximately one half of the volume. The precipitate was filtered and washed with a small volume of cold methanol. This yielded 1.0 g of the piperidine HCl salt as a white solid. The filtrate was concentrated and a small volume of

methanol was added followed by ether. The precipitated material was once again filtered, washed with cold methanol, and dried. This gave an additional 0.49 g of the desired product. Total yield 1.49 g (70%). ^{1}H NMR ($CDCl_3$, 200MHz) δ 7.43-7.20 (m, 3H), 7.10 (dd, 1H), 3.98 (bs, 2H), 3.55-3.40 (bd, 2H), 3.35-3.10 (m, 2H), 2.99 (s, 3H), 2.15 (t, 2H), 2.00 (t, 2H).

Step B: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-[(1,1-dimethylethoxy)carbonyl]amino-2-methyl-propanamide

To 0.35g (1.15 mmol) of (2R)-2-[(1,1-dimethylethoxy)-carbonyl]amino-3-[2-(phenylmethyloxy)ethyl]-1-propanoic acid in 13 mL of dichloromethane was added 1,2-dihydro-1-methanesulfonylspiro-[3H-indole-3,4'-piperdine] hydrochloride (0.325 g; 1.07 mmol), 0.18 mL (1.63 mmol) of N-methylmorpholine, 0.159 g (1.18 mmol) of 1-hydroxybenztriazole(HOBT) and stirred for 15 min. EDC (0.31 g; 1.62 mol) was added and stirring was continued for 1h. An additional 60 μL of N-methylmorpholine was added and stirred for 45 min. The reaction mixture was poured into 5 mL of water and the organic layer was separated. The organic layer was washed with 5 mL of 0.5N aqueous hydrochloric acid and 5 mL of saturated aqueous sodium bicarbonate solution. The combined organics were dried over anhydrous magnesium sulfate, and concentrated to yield 0.627 g of the product as a yellow foam which was used without purification.

To a 0.627 g (1.07 mmol) of the above product in 5 mL of dichloromethane was added 1.0 mL of trifluoroacetic acid and stirred at RT for 75 min. An additional 1.00 mL of trifluoroacetic acid was added and stirred for 10 min. The reaction mixture was concentrated, diluted with 5.0 mL of dichloromethane and carefully basified by pouring into 10 mL of 10% aqueous sodium carbonate solution. The organic layer was separated and the aqueous layer was further extracted with 2X15 mL of dichloromethane. The combined organics were washed with 5 mL of water, dried over potassium carbonate, filtered and concentrated to give

the 0.486 g of the amine as a light yellow foam which was used without purification.

To 0.486 g (1.01 mmol) of the amine and 10 mL of dichloromethane was added 0.26g (1.28 mmol) of 2-[(1,1-dimethyl-ethoxy)carbonyl]amino-2-methyl-propanoic acid, 0.173 g (1.28 mmol) of 1-hydroxybenztriazole (HOBT) and EDC (0.245 g; 1.28 mol) and stirried at RT overnight. The reaction mixture was poured into 5.0 mL of water and the organic layer was separated. The aqueous layer was back extracted with 5 mL of dichloromethane. The combined organics were washed with 5.0 mL of 0.5N aqueous hydrochloric acid, 5 mL of saturated aqueous sodium bicarbonate solution dried over anhydrous magnesium sulfate, and concentrated to yield 0.751 g of the crude product as a yellow foam. A solution of this crude product in dichloromethane was chromatographed on 25 g of silica gel and eluted first with hexanes/acetone/dichloromethane (70/25/5) and then with hexanes/acetone/dichloromethane (65/30/5). This gave 0.63 g of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 400MHz) Compound exists as a 3:2 mixture of rotamers δ 7.40-7.10 (m, 6H), 7.06 (d, 1/3H), 7.02 (t, 1/3H), 6.90 (t, 1/3H), 6.55 (d, 1/3H), 5.15 (m, 1H), 4.95 (bs, 1H), 4.63 (bd, 1/3H), 4.57-4.40 (m, 2 2/3 H), 4.10 (bd, 1/3H), 4.00 (bd, 1/3H), 3.82 (t, 1H), 3.78-3.62 (m, 2H), 3.60-3.50 (m, 1H), 3.04 (q, 1H), 2.87 (s, 1H), 2.86 (s, 2H), 2.80-2.60 (m, 1H), 1.90 (bs, 1H), 2.85-2.75 (m, 1H), 1.82-1.60 (m, 3H), 1.55-1.45 (m, 1H), 1.45 (s, 4H), 1.42 (s, 2H), 1.39 (s, 9H).

Step C: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

To 0.637 g (0.101 mmol) of the intermediate from Step B in 5 mL of dichloromethane was added 2.5 mL of trifluoroacetic acid and stirred at RT for 30 min. The reaction mixture was concentrated to an oil, taken up in 10 mL of ethyl acetate and washed with 8 mL of 10% aqueous sodium carbonate solution. The aqueous layer was further extracted with 5 mL of ethyl acetate. The combined organics were

washed with 10 mL of water, dried over magnesium sulfate, filtered and concentrated to give the 0.512 g of the free base as a white foam.

To 0.512 g of the free base in 5 mL of ethyl acetate at 0°C was added 0.2 mL of saturated hydrochloric acid in ethyl acetate and stirred for 1.5 h. The white precipitate was filtered under nitrogen, washed with ether, and dried to give 0.50 g of the title compound as a white solid ^{1}H NMR (400MHz, CD_3OD) Compound exists as 3:2 mixture of rotamers. δ 7.40-7.28 (m, 4H), 7.25-7.17 (m, 2H), 7.08 (t, 1/3H), 7.00 (t, 1/3H), 6.80 (d, 1/3H), 5.16 (ddd, 1H), 4.60-4.42 (m, 3H), 4.05 (t, 1H), 3.90 (bs, 2H), 3.83-3.70 (m, 2H), 3.30-3.15 (m, 1H0, 2.97 (s, 1H), 2.95 (s, 2H), 2.90-2.78 (m, 1H), 1.96 (t, 1/3H), 1.85-1.65 (m, 4H), 1.63 (s, 2H), 1.60 (s, 4H).

EXAMPLE 3 (METHOD 2)

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl) carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide

Step A: (2R)-[[[-2-(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino-2-(phenylmethoxy)ethyl]-1-propanoic acid allyl ester

Prepared from (2R)-2-[(1,1-dimethylethoxy)carbonyl]-amino-3-(phenylmethyloxy)ethyl-propanoic acid and allyl alcohol by carrying out the coupling reaction in CH_2Cl_2 in the presence of EDC and DMAP. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.25 (s, 5H), 5.8 (m, 1H), 5.2 (dd, 2H), 5.0 (bs, 1H), 4.7 (m, 1H), 4.6 (m, 2H), 4.4 (dd, 2H), 3.9 (dd, 1H), 3.6 (dd, 1H), 1.45 (d, 6H), 1.39 (s, 9H).

Step B: (2R)-[[[-2-(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino-2-(phenylmethyloxy)ethyl)-1-propanoic acid

To a stirred solution of the crude intermediate obtained in Step A (6.7 g, 15.9 mmol), tetrakis (triphenylphosphine)-palladium (1.8 g, 0.1 eq) and, triphenyl phosphine (1.25 g, 0.3 eq) was added a solution

of potassium-2-ethyl hexanoate (35 mL, 0.5M solution in EtOAc). The reaction mixture was stirred at room temperature under nitrogen atmosphere for 1h and then diluted with ether (100 mL) and poured into ice-water. The organic layer was seperated and the aqueous fraction was acidified with citric acid (20%), then extracted with EtOAc. The EtOAc extracts were washed with brine, dried over magnesium sulfate, filtered and evaporated to give the title compound as a solid. ^{1}H NMR (400Hz, CD_3OD) δ 7.3 (s, 5H), 4.7 (m, 1H), 4.5 (s, 2H), 4.0 (m, 1H), 3.6 (m, 1H), 1.4 (d, 6H), 1.3 (s, 9H).

Step C: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-[(1,1-dimethyl-ethoxy)carbonyl]amino-2-methyl-propanamide

To a solution of 1.0 g (3.44 mmol) of 1-methanesulfonyl-spiro[indoline-3,4'-piperidine] hydrochloride, 1.44 g (3.78 mmol) of (2R)-[[-2-(1,1-dimethylethoxy)carbonyl)amino]-2,2-dimethyl-1-oxo-ethyl]-amino-2-(phenylmethyloxy)ethyl)-1-propanoic acid, N-methyl morpholine (0.58 mL; 5.20 mmol), and 1-hydroxybenztriazole (HOBT) (0.58 g; 3.78 mmol), in 50 mL of dichloromethane was added EDC (1.03 g; 5.20 mmol) and stirred at RT for 16h. The reaction mixture was diluted with an additional 50 mL of dichloromethane and washed with aqueous sodium bicarbonate solution (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. Flash chromatography (50 g silica gel) of the crude oily residue gave 2.148 g (90%) of the desired material as a colorless foam. ^{1}H NMR ($CDCl_3$, 400MHz) Compound exists as a 3:2 mixture of rotamers δ 7.40-7.10 (m, 6H), 7.06 (d, 1/3H), 7.02 (t, 1/3H), 6.90 (t, 1/3H), 6.55 (d, 1/3H), 5.15 (m, 1H), 4.95 (bs, 1H), 4.63 (bd, 1/3H), 4.57-4.40 (m, 2 2/3 H), 4.10 (bd, 1/3H), 4.00 (bd, 1/3H), 3.82 (t, 1H), 3.78-3.62 (m, 2H), 3.60-3.50 (m, 1H), 3.04 (q, 1H), 2.87 (s, 1H), 2.86 (s, 2H), 2.80-2.60 (m, 1H), 1.90 (bs, 1H), 2.85-2.75 (m, 1H), 1.82-1.60 (m, 3H), 1.55-1.45 (m, 1H), 1.45 (s, 4H), 1.42 (s, 2H), 1.39 (s, 9H).

Step D: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

To a solution of 2.148 g (3.41 mmol) of the intermediate from Step C in 10 mL of dichloromethane was added 5 mL of trifluoroacetic acid and stirred for 1h. The reaction mixture was concentrated and basified with 100 mL of 5% aqueous sodium carbonate solution and extracted with dichloromethane (3X50 mL). The combined organics were washed with brine (50 mL), dried over anhydrous potassium carbonate, filtered, and concentrated to yield a colorless foam. To a solution of the foam in 25 mL of ethyl acetate at 0°C was added 4 mL of 1M solution of hydrochloric acid in ethyl acetate. The precipitate was filtered and washed first with ethyl acetate and then with ethyl acetate-ether (1:1), dried to yield 1.79 g (93%) of the title compound as a colorless solid. ^{1}H NMR (400MHz, CD_3OD) Compound exists as 3:2 mixture of rotamers. δ 7.40-7.28 (m, 4H), 7.25-7.17 (m, 2H), 7.08 (t, 1/3H), 7.00 (t, 1/3H), 6.80 (d, 1/3H), 5.16 (ddd, 1H), 4.60-4.42 (m, 3H), 4.05 (t, 1H), 3.90 (bs, 2H), 3.83-3.70 (m, 2H), 3.30-3.15 (m, 1H0, 2.97 (s, 1H), 2.95 (s, 2H), 2.90-2.78 (m, 1H), 1.96 (t, 1/3H), 1.85-1.65 (m, 4H), 1.63 (s, 2H), 1.60 (s, 4H).

EXAMPLE 4

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide methanesulfonate

This compound was prepared by the treating the free base obtained in Example 4, Step D, with methane sulfonic acid. The title compound was obtained by recrystallizing it from ethyl acetate-ethanol-water. m.p. = 166°-168°C.

EXAMPLE 5

Procedure for Manufacturing Tablets of 5.0 mg Potency Active Ingredient

Ingredient	Per Tablet	Per 25,000Tablets
Active Ingredient (N-[1(R)-[(1,2-dihydro-1-methane-sulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)-ethyl]-2-amino-2-methylpropanamide methanesulfonate)	5.91 mg	147.8 g
Calcium Phosphate Dibasic	188.10 mg	4.70 kg
Starch Pregelatinized NF 1500	120.00 mg	3.00 kg
Microcrystalline Cellulose NF Avicel PH 101	60.00 mg	1.50 kg
Magnesium Stearate Impalpable Powder NF	2.00 mg	50.0 g
Croscarmellose Sodium NF	24.00 mg	600 g
Ethanol 95%	30 µl	750 ml
Water purified	90 µl	2.25 l
(Tablet Weight = 400 g)		

The active ingredient (equivalent to 5.0 mg anhydrous free base per tablet) was mixed with the calcium phosphate dibasic, the starch pregelatinized NF 1000, the microcrystalline cellulose NF, and half of the croscarmellose sodium NF in a high Fielder 10/25 mixer for about 6 minutes. The 25% ethanol/water granulating solution was slowly added to the powder mixture with the mixer running over a period of about 1.5 minutes then granulated for about 8 minutes to form granules. The wet granules were dried at about 47°C (range 46 to 48°C) in a tray dryer or a fluid bed dryer for approximately 3.0 hours. The dried granules were then milled using a Quadro Comill to achieve fine granules. After milling, the remainder of the croscarmellose sodium NFS was added to the fine granules and mixed in a V blender for about 10 minutes.

Magnesium stearate impalpable powder NF was added to this blend through a 60 mesh stainless steel screen and blended in the V blender for about 1 minute. The lubricated mixture was compressed to provide tablets of 5.0 mg active ingredient (free base equivalent).

EXAMPLE 6

Procedure for Manufacturing Coated Tablets of 5.0 mg Potency Active Ingredient

Ingredient	Per Tablet	Per 25,000 Tablets
Hydroxypropyl Methylcellulose USP (HPMC)	3.2 mg	80 g
Hydroxypropyl Cellulose NF with < 0.3% Silica (HPC)	3.2 mg	80.0 g
Titanium Dioxide USP	1.28 mg	32.0 g
Talc USP Purified	0.32 mg	8.0 g
Water Purified	To 80 µl	To 200 ml
(Film Coated Tablet Weight = 408 g)		

The titanium dioxide and talc, USP were mixed and passed through a 60 mesh stainless steel screen. This mixture was mixed with HPMC and HPC to form a dry blend. The dry blend was added to water (20 ml) which was previously heated to 90°C with mild agitation to ensure that the blend is wetted to form a slurry. The remainder of the water (up to 32 ml) was added to the slurry at ambient temperature with gentle agitation to form a suspension. The suspension was then applied to the tablets from the previous Example using the following guidelines to provide the coated tablets.

Pan: suitable size
Pan Speed: 20 RPM
Nozzles: 2850 liquid/120 air
Inlet Temperature: 85°C
Bed Temperature: 47°C
Spray Rate: ca. 2.0 g/minute/kg Tablets

EXAMPLE 7

Procedure for Manufacturing Tablets of 25 mg Potency Active Ingredient

Ingredient	Per Tablet	Per 25,000Tablets
Active Ingredient (N-[1(R)-[(1,2-dihydro-1-methane-sulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)-ethyl]-2-amino-2-methylpropanamide methanesulfonate)	29.55 mg	738.75 g
Calcium Phosphate Dibasic	174.46 mg	4.361 kg
Starch Pregelatinized NF 1500	113.00 mg	2.825 kg
Microcrystalline Cellulose NF Avicel PH 101	57.00 mg	1.425 kg
Magnesium Stearate Impalpable Powder NF	2.00 mg	50.0 g
Croscarmellose Sodium NF	24.00 mg	600 g
Ethanol 95%	30 µl	750 ml
Water purified (Tablet Weight = 400 g)	90 µl	2.25 l

The active ingredient (equivalent to 25 mg anhydrous free base per tablet) was mixed with the calcium phosphate dibasic, the starch pregelatinized NF 1000, the microcrystalline cellulose NF, and half of the croscarmellose sodium NF in a high shear granulator Fielder 10/25 mixer for about 6 minutes. The 25% ethanol/water granulating solution was slowly added to the powder mixture with the mixer running over a period of about 1.5 minutes then granulated for about 8 minutes to form

granules. The wet granules were dried at about 47°C (range 46 to 48°C) in a tray dryer or a fluid bed dryer for approximately 3.0 hours. The dried granules were then milled using a Quadro Comill to achieve fine granules. After milling, the remainder of the croscarmellose sodium NFS was added to the fine granules and mixed in a V blender for about 10 minutes. Magnesium stearate impalpable powder NF was added to this blend through a 60 mesh stainless steel screen and blended in the V blender for about 1 minute. The lubricated mixture was compressed to provide tablets of 25 mg active ingredient (free base equivalent).

EXAMPLE 8

Procedure for Manufacturing Coated Tablets of 25 mg Potency Active Ingredient

Ingredient	Per Tablet	Per 25,000 Tablets
Hydroxypropyl Methylcellulose USP (HPMC)	3.2 mg	80 g
Hydroxypropyl Cellulose NF with < 0.3% Silica (HPC)	3.2 mg	80.0 g
Titanium Dioxide USP	1.28 mg	32.0 g
Talc USP Purified	0.32 mg	8.0 g
Water Purified (Film Coated Tablet Weight = 408 g)	To 80 µl	To 200 ml

Using essentially the procedure of Example 9 and applying the suspension to the tablets from the previous Example, 25 mg potency coated tablets were formed.

EXAMPLE 12

Clinical Study of N-[1(R)-[(1,2-Dihydro-1-methane-sulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenyl-methyloxy)ethyl]-2-amino-2-methylpropanamide methanesulfonate in Healthy Young Adults

In this study, 9 healthy young men (ages 18 to 30 years) who did not suffer sleep complaints were randomly assigned to a sequence of 3 treatment periods. In each period the subjects received a single oral dose of either placebo, 5 mg of N-[1(R)-[(1,2-dihydro-1-methane-sulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyl-oxy)ethyl]-2-amino-2-methyl-propanamide methanesulfonate or 25 mg of N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methyl-propanamide methanesulfonate once daily for 7 days. Sleep was recorded for 2 nights: a habituation night and a blood sampling night (Days 6 and 7 of study drug administration). On average, the durations of Stages 1, 2, and 3 were similar in the three study conditions. After 7 days of treatment, however, Stage 4 sleep duration was significantly higher after administration of 25 mg of N-[1(R)-[(1,2-dihydro-1-methane-sulfonyl-spiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyl-oxy)ethyl]-2-amino-2-methylpropanamide methanesulfonate than after treatment with placebo (54 ± 27 min versus 37 ± 19 min, $N = 8$, $p < 0.05$). Moreover, when compared to placebo, there was a significant increase in REM sleep in the 25 mg treatment group on the blood sampling night (103 ± 9 min versus 88 ± 19 min, $N = 9$, $p < 0.05$) and there was a reduction in sleep latency, a reduction in the amount of time spent awake, as well as a decrease in the number of sleep disturbances in the 25 mg treatment group. Accordingly, the group treated with 25 mg of growth hormone secretagogue exhibited improved sleep efficiency and sleep maintenance. This study suggests that use of a growth hormone secretagogue may have a beneficial effect in enhancing the quality of sleep in humans.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A method for enhancing the quality of sleep in a mammal which comprises administering an effective amount of a growth hormone secretagogue.

2. The method of Claim 1 wherein the growth hormone secretagogue is an orally active growth hormone secretagogue.

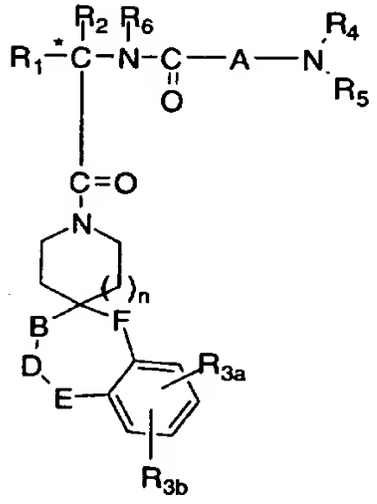
3. The method of Claim 2 wherein the growth hormone secretagogue is orally administered.

4. The method of Claim 1 wherein the growth hormone secretagogue is a non-peptidal growth hormone secretagogue.

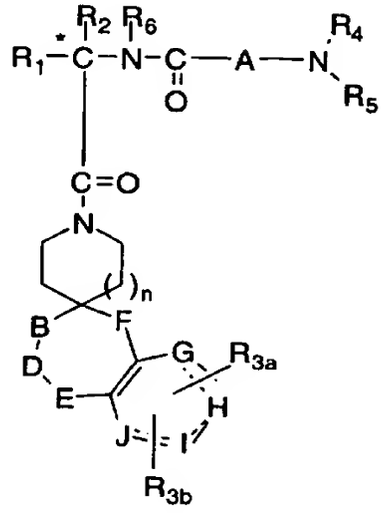
5. The method of Claim 1 wherein the mammal is a human.

6. The method of Claim 4 wherein the growth horomone secretagogue is able to induce the engogenous release of growth hormone or growth hormone-releasing hormone in the first few hours following sleep onset, or alternatively in the period immediately preceding sleep onset.

7. The method of Claim 1 wherein the growth hormone secretagogue is selected from the group consisting of:



Formula I



Formula II

wherein:

R1 is selected from the group consisting of:

-C1-C10 alkyl, -aryl, -aryl-(C1-C6 alkyl),

-C3-C7 cycloalkyl-(C1-C6alkyl), -C1-C5alkyl-K-C1-C5 alkyl, -aryl(C0-C5alkyl)-K-(C1-C5 alkyl),

-C3-C7 cycloalkyl(C0-C5 alkyl)-K-(C1-C5 alkyl),

wherein K is O, S(O)m, N(R2)C(O), C(O)N(R2), OC(O), C(O)O, or -CR2=CR2-, or -C≡C-,

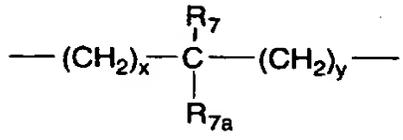
and wherein the aryl groups are as defined below and the R2 and alkyl groups may be futher substituted by 1 to 9 halogen, S(O)mR2a, 1 to 3 OR2a, or C(O)OR2a, and the aryl groups may be further substituted by phenyl, phenoxy, halophenyl, 1-3 C1-C6 alkyl, 1 to 3 halogen, 1 to 2 -OR2, methylenedioxy, -S(O)mR2, 1 to 2 -CF3, -OCF3, nitro, -N(R2)(R2), -N(R2)C(O)R2, -C(O)OR2, -C(O)N(R2)(R2), -SO2N(R2)(R2), -N(R2)S(O)2 aryl, and -N(R2)SO2R2;

R_2 is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_3-C_8 cyclic ring optionally including oxygen, sulfur or NR_{2a};
R_{2a} is hydrogen, or C_1-C_6 alkyl;

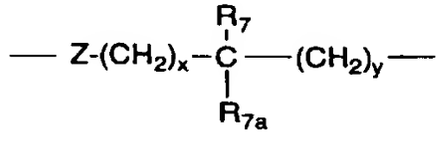
R_{3a} and R_{3b} are independently selected from the group consisting of: hydrogen, halogen, -C_1-C_6 alkyl, -OR_2, cyano, -OCF_3, methylenedioxy, nitro, -$S(O)_mR$, -CF_3 or -$C(O)OR_2$ and when R_{3a} and R_{3b} are in an ortho arrangement, they may be joined to form a C_5 to C_8 aliphatic or aromatic ring optionally including 1 or 2 heteroatoms selected from oxygen, sulfur or nitrogen;

R_4 and R_5 are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, substituted C_1-C_6 alkyl wherein the substituents are selected from 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy, 2-furyl, C_1-C_6 alkoxycarbonyl, -$S(O)_m$(C_1-C_6 alkyl); or R_4 and R_5 can be taken together to form -$(CH_2)_rL_a(CH_2)_s$- where L_a is -$C(R_2)_2$-, -O-, -$S(O)_m$-, or -$N(R_2)$-, where r and s are independently 1 to 3 and R_2 is as defined above;
R_6 is hydrogen or C_1-C_6 alkyl;

A is:



or



wherein x and y are independently 0-3;
Z is N-R_2 or O;

R_7 and R_{7a} are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, -OR_2, trifluoromethyl, phenyl, substituted C_1-C_6 alkyl where the substituents are selected from imidazolyl, phenyl, indolyl, p-hydroxyphenyl, -OR_2, 1 to 3 fluoro, -$S(O)_mR_2$, -$C(O)OR_2$, -C_3-C_7 cycloalkyl, -$N(R_2)(R_2)$, -$C(O)N(R_2)(R_2)$; or R_7 and R_{7a} can independently be joined to one or both of R_4 and R_5 groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms;

B, D, E, and F are independently selected from the group consisting of: -$C(R_8)(R_{10})$-, -O-, C=O, -$S(O)_m$-, or -NR_9-, such that one or two of B, D, E, or F may be optionally absent to provide a 5, 6, or 7 membered ring; and provided that B, D, E and F can be -$C(R_8)(R_{10})$- or C=O only when one of the remaining B, D, E and F groups is simultaneously -O-, -$S(O)_m$-, or -NR_9-, or
B and D, or D and E taken together may be -N=CR_{10}- or -CR_{10}=N-, or B and D, or D and E taken together may be -CR_8=CR_{10}-, provided one of the other of B and E or F is simultaneously -O-, -$S(O)_m$-, or -NR_9;

R_8 and R_{10} are independently selected from the group consisting of: hydrogen, -R_2, -OR_2, -$(CH_2)_q$-aryl, -$(CH_2)_q$-$C(O)OR_2$, -$(CH_2)_q$-$C(O)O(CH_2)_q$-aryl, or -$(CH_2)_q$-(1H-tetrazol-5-yl), where the aryl may be optionally substituted by 1 to 3 halo, 1 to 2 C_1-C_8 alkyl, 1 to 3 -OR_2 or 1 to 2 -$C(O)OR_2$;

R_9 is selected from the group consisting of:
-R_2, -$(CH_2)_q$-aryl, -$C(O)R_2$, -$C(O)(CH_2)_q$-aryl, -SO_2R_2, -$SO_2(CH_2)_q$-aryl, -$C(O)N(R_2)(R_2)$, -$C(O)N(R_2)(CH_2)_q$-aryl, -$C(O)OR_2$, 1-H-tetrazol-5-yl, -SO_3H, -$SO_2NHC{\equiv}N$, -$SO_2N(R_2)$aryl, -$SO_2N(R_2)(R_2)$,

and wherein the $(CH_2)_q$ may be optionally substituted by 1 to 2 C_1-C_4 alkyl, and the R_2 and aryl may be optionally further substituted by 1 to 3 $-OR_{2a}$, $-O(CH_2)_q$ aryl, 1 to 2 $-C(O)OR_{2a}$, 1 to 2 $-C(O)O(CH_2)_q$ aryl, 1 to 2 $-C(O)N(R_{2a})(R_{2a})$, 1 to 2 $-C(O)N(R_{2a})(CH_2)_q$ aryl, 1 to 5 halogen, 1 to 3 C_1-C_4 alkyl, 1,2,4-triazolyl, 1-H-tetrazol-5-yl, $-C(O)NHSO_2R_{2a}$, $-S(O)_mR_{2a}$, $-C(O)NHSO_2(CH_2)q$-aryl, $-SO_2NHC{\equiv}N$, $-SO_2NHC(O)R_{2a}$, $-SO_2NHC(O)(CH_2)_q$aryl, $-N(R_2)C(O)N(R_{2a})(R_{2a})$, $-N(R_{2a})C(O)N(R_{2a})(CH_2)_q$-aryl, $-N(R_{2a})(R_{2a})$, $-N(R_{2a})C(O)R_{2a}$, $-N(R_{2a})C(O)(CH_2)q$ aryl, $-OC(O)N(R_{2a})(R_{2a})$, $-OC(O)N(R_{2a})(CH_2)_q$ aryl, $-SO_2(CH_2)_qCONH$-(CH_2)wNHC(O)R_{11}, wherein w is 2-6 and R_{11} may be biotin, aryl, or aryl substituted by 1 or 2 OR_2, 1-2 halogen, azido or nitro;

m is 0, 1 or 2;

n is 1, or 2;

q may optionally be 0, 1, 2, 3, or 4; and

G, H, I and J are carbon, nitrogen, sulfur or oxygen atoms, such that at least one is a heteroatom and one of G, H, I or J may be optionally missing to afford a 5 or 6 membered heterocyclic aromatic ring; and pharmaceutically acceptable salts and individual diastereomers thereof.

8. The method of Claim 1 wherein the growth hormone secretagogue is selected from the group consisting of:

1) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

2) N-[1(R)-[(1,2-Dihydro-1-methanecarbonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

3) N-[1(R)-[(1,2-Dihydro-1-benzenesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

4) N-[1(R)-[(3,4-Dihydro-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl) carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

5) N-[1(R)-[(2-Acetyl-1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

6) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

7) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide methanesulfonate;

8) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

9) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

10) N-[1(S)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethylthio)ethyl]-2-amino-2-methylpropanamide;

11) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide;

12) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methyl-propanamide;

13) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-4-phenylbutyl]-2-amino-2-methyl-propanamide;

14) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

15) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

16) N-[1(R)-[(1,2-Dihydro-1-(2-ethoxycarbonyl)methylsulfonylspiro-[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

17) N-[1(R)-[(1,2-Dihydro-1,1-dioxospiro[3H-benzothiophene-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

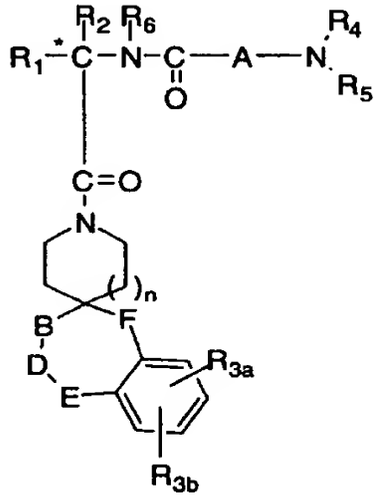
and pharmaceutically acceptable salts thereof.

9. The method of Claim 4 wherein the compound is administered in conjunction with an additional growth hormone secretagogue which is selected from the group consisting of: GHRP-6, GHRP-1, GHRP-2, growth hormone releasing factor; an analog of growth hormone releasing factor; IGF-1; and IGF-2.

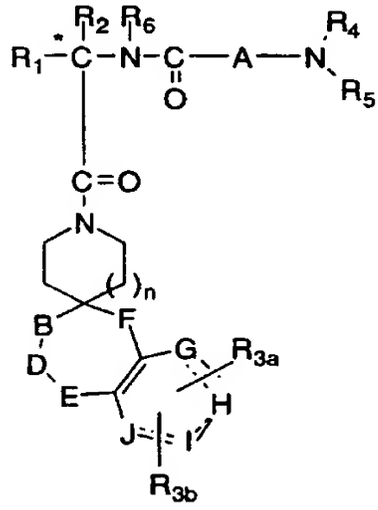
10. A method for enhancing the quality of sleep in a mammal which comprises administering an effective amount of a growth hormone secretagogue in combination with a compound which is selected from the group consisting of: adinazolam, allobarbital, alonimid, alprazolam, amitriptyline, amobarbital, amoxapine, bentazepam, benzoctamine, brotizolam, bupropion, busprione, butabarbital, butalbital, capuride, carbocloral, chloral betaine, chloral hydrate, chlordiazepoxide, clomipramine, cloperidone, clorazepate, clorethate, clozapine, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, estazolam, ethchlorvynol, etomidate, fenobam, flunitrazepam, flurazepam, fluvoxamine, fluoxetine, fosazepam, glutethimide, halazepam, hydroxyzine, imipramine, lithium, lorazepam, lormetazepam, maprotiline, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, midaflur, midazolam, nefazodone, nisobamate, nitrazepam, nortriptyline, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, reclazepam, roletamide, secobarbital, sertraline, suproclone, temazepam, thioridazine, tracazolate, tranylcypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, zolazepam, zolpidem, and salts thereof.

11. The method of Claim 10 wherein the mammal is a human.

12. The method of Claim 10 wherein the growth hormone secretagogue is selected from the group consisting of:



Formula I



Formula II

wherein:

R_1 is selected from the group consisting of:

$-C_1$-C_{10} alkyl, -aryl, -aryl-(C_1-C_6 alkyl),

-C_3-C_7 cycloalkyl-(C_1-C_6alkyl), -C_1-C_5alkyl-K-C_1-C_5 alkyl, -aryl(C_0-C_5alkyl)-K-(C_1-C_5 alkyl),

-C_3-C_7 cycloalkyl(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl),

wherein K is O, $S(O)_m$, $N(R_2)C(O)$, $C(O)N(R_2)$, OC(O), C(O)O, or $-CR_2=CR_2-$, or -C≡C-,

and wherein the aryl groups are as defined below and the R_2 and alkyl groups may be futher substituted by 1 to 9 halogen, $S(O)mR_{2a}$, 1 to 3 OR_{2a}, or $C(O)OR_{2a}$, and the aryl groups may be further substituted by phenyl, phenoxy, halophenyl, 1-3 C_1-C_6 alkyl, 1 to 3 halogen, 1 to 2 $-OR_2$, m thylenedioxy, $-S(O)_mR_2$, 1 to 2 $-CF_3$, $-OCF_3$, nitro,

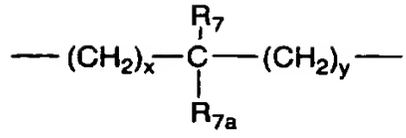
-$N(R_2)(R_2)$, -$N(R_2)C(O)R_2$, -$C(O)OR_2$, -$C(O)N(R_2)(R_2)$, -$SO_2N(R_2)(R_2)$, -$N(R_2)S(O)_2$ aryl, and -$N(R_2)SO_2R_2$;

R_2 is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_3-C_8 cyclic ring optionally including oxygen, sulfur or NR_{2a};
R_{2a} is hydrogen, or C_1-C_6 alkyl;

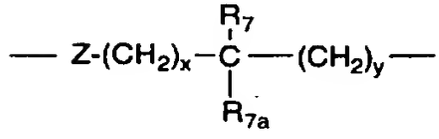
R_{3a} and R_{3b} are independently selected from the group consisting of: hydrogen, halogen, -C_1-C_6 alkyl, -OR_2, cyano, -OCF_3, methylenedioxy, nitro, -$S(O)_mR$, -CF_3 or -$C(O)OR_2$ and when R_{3a} and R_{3b} are in an ortho arrangement, they may be joined to form a C_5 to C_8 aliphatic or aromatic ring optionally including 1 or 2 heteroatoms selected from oxygen, sulfur or nitrogen;

R_4 and R_5 are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, substituted C_1-C_6 alkyl wherein the substituents are selected from 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy, 2-furyl, C_1-C_6 alkoxycarbonyl, -$S(O)_m(C_1$-C_6 alkyl); or R_4 and R_5 can be taken together to form -$(CH_2)_rL_a(CH_2)_s$- where L_a is -$C(R_2)_2$-, -O-, -$S(O)_m$-, or -$N(R_2)$-, where r and s are independently 1 to 3 and R_2 is as defined above;
R_6 is hydrogen or C_1-C_6 alkyl;

A is:



or



wherein x and y are independently 0-3;
Z is N-R_2 or O;

R_7 and R_{7a} are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, -OR_2, trifluoromethyl, phenyl, substituted C_1-C_6 alkyl where the substituents are selected from imidazolyl, phenyl, indolyl, p-hydroxyphenyl, -OR_2, 1 to 3 fluoro, -$S(O)_mR_2$, -$C(O)OR_2$, -C_3-C_7 cycloalkyl, -$N(R_2)(R_2)$, -$C(O)N(R_2)(R_2)$; or R_7 and R_{7a} can independently be joined to one or both of R_4 and R_5 groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms;

B, D, E, and F are independently selected from the group consisting of: -$C(R_8)(R_{10})$-, -O-, C=O, -$S(O)_m$-, or -NR_9-, such that one or two of B, D, E, or F may be optionally absent to provide a 5, 6, or 7 membered ring; and provided that B, D, E and F can be -$C(R_8)(R_{10})$- or C=O only when one of the remaining B, D, E and F groups is simultaneously -O-, -$S(O)_m$-, or -NR_9-, or
B and D, or D and E taken together may be -N=CR_{10}- or -CR_{10}=N-, or B and D, or D and E taken together may be -CR_8=CR_{10}-, provided one of the other of B and E or F is simultaneously -O-, -$S(O)_m$-, or -NR_9;

R_8 and R_{10} are independently selected from the group consisting of: hydrogen, -R_2, -OR_2, (-CH_2)$_q$-aryl, -(CH_2)$_q$-C(O)OR_2, -(CH_2)$_q$-C(O)O(CH_2)$_q$-aryl, or -(CH_2)$_q$-(1H-tetrazol-5-yl), where the aryl may be optionally substituted by 1 to 3 halo, 1 to 2 C_1-C_8 alkyl, 1 to 3 -OR_2 or 1 to 2 -C(O)OR_2;

R_9 is selected from the group consisting of:
-R_2, -(CH_2)$_q$-aryl, -C(O)R_2, -C(O)(CH_2)$_q$-aryl, -SO_2R_2, -SO_2(CH_2)$_q$-aryl, -C(O)N(R_2)(R_2), -C(O)N(R_2)(CH_2)$_q$-aryl, -C(O)OR_2, 1-H-tetrazol-5-yl, -SO_3H, -SO_2NHC≡N, -SO_2N(R_2)aryl, -SO_2N(R_2)(R_2),
and wherein the (CH_2)$_q$ may be optionally substituted by 1 to 2 C_1-C_4 alkyl, and the R_2 and aryl may be optionally further substituted by 1 to 3 -OR_{2a}, -O(CH_2)$_q$ aryl, 1 to 2 -C(O)OR_{2a}, 1 to 2 -C(O)O(CH_2)$_q$ aryl, 1 to 2 -C(O)N(R_{2a})(R_{2a}), 1 to 2 -C(O)N(R_{2a})(CH_2)$_q$ aryl, 1 to 5 halogen, 1 to 3 C_1-C_4 alkyl, 1,2,4-triazolyl, 1-H-tetrazol-5-yl, -C(O)NHSO_2R_{2a}, -S(O)$_m R_{2a}$, -C(O)NHSO_2(CH_2)$_q$-aryl, -SO_2NHC≡N, -SO_2NHC(O)R_{2a}, -SO_2NHC(O)(CH_2)$_q$aryl, -N(R_2)C(O)N(R_{2a})(R_{2a}), -N(R_{2a})C(O)N(R_{2a})(CH_2)$_q$-aryl, -N(R_{2a})(R_{2a}), -N(R_{2a})C(O)R_{2a}, -N(R_{2a})C(O)(CH_2)$_q$ aryl, -OC(O)N(R_{2a})(R_{2a}), -OC(O)N(R_{2a})(CH_2)$_q$ aryl, -SO_2(CH_2)$_q$CONH-(CH_2)$_w$NHC(O)R_{11},
wherein w is 2-6 and R_{11} may be biotin, aryl, or aryl substituted by 1 or 2 OR_2, 1-2 halogen, azido or nitro;

m is 0, 1 or 2;
n is 1, or 2;
q may optionally be 0, 1, 2, 3, or 4; and
G, H, I and J are carbon, nitrogen, sulfur or oxygen atoms, such that at least one is a heteroatom and one of G, H, I or J may be optionally missing to afford a 5 or 6 membered heterocyclic aromatic ring;

and pharmaceutically acceptable salts and individual diastereomers thereof.

13. The method of Claim 10 wherein the growth hormone secretagogue is selected from the group consisting of:

1) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

2) N-[1(R)-[(1,2-Dihydro-1-methanecarbonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

3) N-[1(R)-[(1,2-Dihydro-1-benzenesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

4) N-[1(R)-[(3,4-Dihydro-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl) carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

5) N-[1(R)-[(2-Acetyl-1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

6) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

7) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide methanesulfonate;

8) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

9) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

10) N-[1(S)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethylthio)ethyl]-2-amino-2-methylpropanamide;

11) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide;

12) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methyl-propanamide;

13) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-4-phenylbutyl]-2-amino-2-methyl-propanamide;

14) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

15) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

16) N-[1(R)-[(1,2-Dihydro-1-(2-ethoxycarbonyl)methylsulfonylspiro-[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

17) N-[1(R)-[(1,2-Dihydro-1,1-dioxospiro[3H-benzothiophene-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

and pharmaceutically acceptable salts thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/07516

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 38/00, 31/44
US CL :514/16, 17, 278

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/16, 17, 278

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Registry, CAPlus, HcaPlus, UsPatfull, Biosis, WPiDS, Medline, Embase, Biotechds

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MCGAULEY, G. Growth hormone treatment, brain neurotransmitters and thyroxine. Clinical Endocrinology. 05 March 1996, Volume 44, pages 325-326, see entire document.	1-13
A	BURMAN et al. Growth hormone treatment affects brain neurotransmitters and thyroxine. Clinical Endocrinology. 05 March 1996, Volume 44, pages 319-324, see entire document.	1-13
Y	FRANZ et al. Growth hormone secretion timing in depression: clinical outcome comparisons. Biological Psychiatry. 1995, Volume 38, pages 720-729, see abstract.	1-13

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

06 AUGUST 1997

Date of mailing of the international search report

03 SEP 1997

Name and mailing address of the ISA/US
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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/07516

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FIASCHE et al. Growth hormone neurosecretory disfunction in major depressive illness. Psychoneuoroendocrinology. 1995, Volume 20, Number 7, pages 727-733, see abstract.	1-13
A	US 5,284,841 A (CHU et al) 08 February 1994, see columns 2-12 and 48.	1-13
A	US 5,310,737 A (FISHER et al) 10 May 1994, see columns 2-11 and 31.	1-13
X, P	US 5,536,716 A (CHEN et al) 16 July 1996, see columns 2-10 and 36.	1-13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/07516

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-6 and 9-11 (in part)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The claims are unduly broad. They were searched only to the extent that the growth hormone secretagogue is a peptide disclosed in the description or the compounds of Formula I or Formula II as found in claims 8 and 14.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

Group I, claims 1-6, 9-11, each in part, directed to a method for enhancing the quality of sleep in a mammal which comprises administering effecting amount of a growth hormone secretagogue when said secretagogue is a peptide.

Group II, claims 1-6, 9-11, each in part and 7-8, 12-13, directed to the method of claim one when said secretagogue is the compound of formula I.

Group III, claims 1-6, 9-11, each in part and 7-8, 12-13, directed to the method of claim one when said secretagogue is the compound of formula II.

The claims fail to show a single general inventive concept under PCT Rule 13.2 as the inventions described therein fail to possess any "special technical feature" that define a contribution which each of the compounds makes over the prior art. PCT Rules 13.1 and 13.2 do not provide for multiple distinct compounds within a single inventive concept, and the method, as disclosed in the description, encompasses said compounds.